# The Metabolic Effects of Orlistat and Rosiglitazone on Insulin Action in a Group of Chinese Patients Affected by the Metabolic Syndrome

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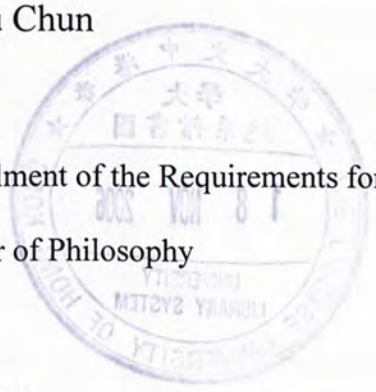

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Co-Supervisor: Professor Brian Tomlinson



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## ABSTRACT

**The Metabolic Effects of Orlistat and Rosiglitazone on Insulin action in a group of Chinese Patients affected by the Metabolic Syndrome**

submitted by

**LOH Shwu Chun**

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at

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Individuals with the metabolic syndrome are at increased risk for developing diabetes mellitus and cardiovascular disease. They also have an increased mortality from cardiovascular diseases and all causes. Current concepts of the metabolic syndrome represent the convergence of two merging streams of research. Some investigators viewed the metabolic syndrome as a result of obesity and its metabolic complications. On the other hand, insulin resistance is perceived as the major underlying cause for the metabolic syndrome.

Although the effects of pharmacotherapy on improving the metabolic syndrome are widely investigated overseas, local work is relatively lacking. This study aimed to examine the effects and assess the changes of cardiovascular risk factors of orlistat and rosiglitazone in a group of Chinese patients affected by the metabolic syndrome. Both agents do not reduce plasma glucose levels directly. Instead, they act by either directly increasing the body's insulin sensitivity as for rosiglitazone, or indirectly by reducing body weight leading eventually to improved metabolic control as for orlistat.

A prospective, 6-months randomized single-blinded placebo-controlled study was conducted involving 63 Chinese participants with type 2 diabetes or impaired glucose tolerance, aged > 18 years with a BMI $\geq$ 23kg/m$^2$ were administered orally 120 mg orlistat three times daily, rosiglitazone 2mg twice daily or placebo three times daily. Changes in clinical and metabolic parameters indicative of the metabolic

syndrome were monitored, including body weight, glycaemic control, lipid levels and drug tolerability.

There were 20 individuals in the rosiglitazone group and 19 individuals in both the orlistat and placebo groups. The orlistat group demonstrated improved lipid profiles, especially on the reduction of total cholesterol (12% $p \leq 0.0005$) and LDL-cholesterol (21%, $p = 0.0002$). This was accompanied by an improvement in the fasting insulin levels ($p = 0.07$) and HOMA scores ($p = 0.026$). In comparison, the rosiglitazone group exhibits maximum improvements in fasting insulin ($p = 0.004$), 2hr-post OGTT insulin ($p = 0.004$) and HOMA scores ($p = 0.005$). However, there is an increase from baseline in the LDL-cholesterol levels (12%), body fat (3.7%) and hip circumference (1.5%).

To prevent progression to type 2 diabetes mellitus and its complications, early detection and implementation of appropriate treatment strategies for the metabolic syndrome is crucial. Other than dietary therapy and exercise, the use of rosiglitazone especially in the treatment of insulin-resistant patients with IGT or type 2 diabetes is practical, since most of its problems derived from insulin resistance. On the other hand, orlistat, with its effects on weight, lipids and glucose, may be a useful treatment modality, especially in obese patients insulin-resistant patients.

# 中文摘要

## 賽尼可(Orlistat)及羅西格列酮(Rosiglitazone)對華裔新陳代謝綜合症患者胰島素功能之作用

羅淑珍

新陳代謝綜合症患者患上糖尿病與心血管的疾病的機會比較高。而他們因心血管的疾病或所有因素所造成的死亡率也比較高。目前對新陳代謝綜合症的看法是由兩派研究合併而成。有些研究員認爲新陳代謝綜合症是因爲痴肥與其新陳代謝併發症所造成的。而另一種看法把胰島素抵抗性當成是新陳代謝綜合症的主要潛在因素。

雖然國外已廣泛的研究藥物療效對於改善新陳代謝綜合症的效果，相比之下，本地的研究仍然缺乏。此研究目的是要調察賽尼可及羅西格列酮對於一組受新陳代謝綜合症影響的華裔病人的效果及確定對心血管疾病風險。此兩種藥物並不直接減少血糖。羅西格列酮直接影響體內的胰島素敏感度，而賽尼可卻間接的通過減少體重，進而使到新陳代謝的控制受到改善。

六十三位十八歲以上，體重指標 ≥ 23kg/m$^2$, 並患有第二型糖尿病或葡萄糖耐量底的華裔參加了一項爲期六個月的隨機單盲安慰劑對照之臨床研究。參加者每日需服食三次 120mg 賽尼可、賽尼可安慰劑或每日服食兩次 2mg 羅西格列酮。這期間會觀察代表新陳代謝綜合症的臨床與新陳代謝參數如體重，血糖及血脂與對藥物的反應。

羅西格列酮的組別有二十人，賽尼可與安慰劑的組別各有十九人。賽尼可的組別對於血脂方面有顯著的改善，尤其在於減少總膽固醇與低密度脂蛋百膽固醇。同時，空腹胰島素與代表胰島素抗體的 HOMA 分數也有進步。相比之下，羅西格列酮的組別對於血糖指數如空腹胰島與 HOMA 分數有著顯著的改善。但是，低密度脂蛋百膽固醇、體脂、坐圍卻比基綫增加了。

為避免患上新陳代謝綜合症演變成糖尿病與其併發症，關鍵在於提早發現並施行適當的治療方針。既然新陳代謝綜合症主要的問題在與胰島素抗體，除了飲食方面的治療與多作運動，以羅西格列酮治療患有第二型糖尿病或葡萄糖耐量底的病人是實際的。而賽尼可在體重，血脂與血糖的影響，對於癡肥病人可成爲有用的治療方針。

# Abbreviations

| | |
|---|---|
| AACE | American Association of Clinical Endocrinologists |
| ADA | American Diabetes Association |
| ADP | Adenosine Diphosphate |
| ALT | Alanine Transaminase |
| AST | Aspartate Aminotransferase |
| ATP | Adenosine Triphosphate |
| ATP III | The Adult Treatment Panel III of the National Cholesterol Education Program |
| AUC | Area Under the Curve |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CAD | Coronary Artery Disease |
| D.O.B. | Date of Birth |
| DPP | Diabetes Prevention Program |
| DPS | Diabetes Preventive Study |
| EGIR | European Group for the Study of Insulin Resistance |
| ELISA | Enzyme-linked Immunosorbent Assay |
| FPG | Fasting Plasma Glucose |
| G-6-P | Glucose-6-Phosphate |
| G-6-PDH | Glucose-6-Phosphate Dehydrogenase |
| Gluconate-6-P | Gluconate-6-Phosphate |

| | |
|---|---|
| H+ | Hydrogen ions |
| Hb1Ac | Glycosylated Haemoglobin |
| HDL-cholesterol | High-density Lipoproten Cholesterol |
| HOMA | Homeostatic Model Assessment |
| IDF | International Diabetes Federation |
| IFG | Impaired Fasting Glucose |
| IGF-I | Insulin-like Growth Factor-I |
| IGT | Impaired Glucose Tolerance |
| LCCA | Left Common Carotid Artery |
| LDL-cholesterol | Low-density Lipoproten Cholesterol |
| NADP | Nicotinamide adenine dinucleotide phosphate |
| NAPDH | Reduced nicotinamide adenine dinucleotide phosphate |
| NCEP | National Cholesterol Education Program |
| OGTT | Oral Glucose Tolerance Test |
| PPAR | Peroxisome Proliferator-Activated Receptor |
| RCCA | Right Common Carotid Artery |
| STOP-NIDDM | Study to Prevent Non-Insulin dependent diabetes mellitus |
| TLC | Therapeutic lifestyle Changes |
| UKPDS | United Kingdom Prospective Diabetes Study |
| VLDL | Very-low density Lipoprotein Cholesterol |
| WHO | World Health Organisation |

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# Introduction

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# Introduction

# 1 Introduction

Over the last decade, investigators have given increased attention to the complex role of multiple metabolic abnormalities in the development of related chronic diseases such as type 2 diabetes mellitus and cardiovascular disease. One of the first people to introduce the metabolic syndrome in scientific literature was Camus in 1966. However, this entity did not receive much interest until Reaven in 1988, introduced the term "Syndrome X", which referred to a group of related disorders, associated with increased risk of both type 2 diabetes and cardiovascular disease, characterised by impaired glucose tolerance, dyslipidaemia and hypertension.

Insulin resistance, located primarily in skeletal muscle and limited to non-oxidative glucose disposal was cited as the primary underlying mechanism of the syndrome. Insulin resistance is an impaired biological response to the effects of exogenous or endogenous insulin (on glucose, lipids, metabolic activity or vascular endothelial function). Hyperinsulinaemia, which accompanies insulin resistance, can maintain sufficiently normal glucose metabolism as long as pancreatic β-cell function remains normal. However, in many patients, β-cell deficiencies slowly develop and type 2 diabetes occurs as a result of impaired glucose metabolism. (Alberti KG et al. 1998).

The combination of insulin resistance and compensatory hyperinsulinaemia were considered necessary for the development of other lipid and non-lipid abnormalities. DeFronzo and Ferrannini 1991 also stated insulin resistance as the central feature of the syndrome. Syndrome X is also known as to as the metabolic syndrome, the metabolic cardiovascular syndrome, atherothrombogenic syndrome, the insulin resistance syndrome or plurimetabolic syndrome. However, the terms "insulin resistance" or "metabolic syndrome" are now most widely accepted for this clinical entity. For the purposes of this thesis, the metabolic syndrome will be adopted.

## 1.1 Definition and diagnostic criteria of the metabolic syndrome

Although it has been the subject of intense discussion for several years, there is still no easy definition for the metabolic syndrome as it is not a unique clinical disease. Rather, it is a metabolic milieu whereby a number of cardiovascular risk factors arise and interact synergistically.

Several expert panels have recently provided some uniformity by proposing similar metabolic components within the syndrome (Table 1.1). Although these guidelines are consistent in that there is a focus on insulin resistance/hyperinsulinaemia, hyperglycaemia, obesity (especially central/upper body distribution), dyslipidaemia and hypertension as constituent traits there is still

## Table 1.1 : Clinical Identification of The Metabolic Syndrome

| **Risk Factor** | **NCEP/ATP III (2001)** *3 risk factors or more* | **WHO Definition (1999)** *2 risk factors or more* | **AACE Definition (2003)** *Diagnosis depends on clinical judgement* | **EGIR Definition (2002)** *Fasting hyperinsulinaemia with 2 or more risk factors* |
|---|---|---|---|---|
| Obesity (abdominal obesity) | Waist circumference<br>> 102 cm (Male)<br>> 88 cm (Female) | BMI > 30 kg/m2 **OR**<br>W/H > 0.9 (Male);<br>> 0.85 (Female) | Overweight/Obesity:<br>BMI ≥ 25 kg/m2 | Waist circumference<br>> 94 cm (Male)<br>> 80 cm (Female) |
| Insulin resistance or Glucose intolerance | FPG ≥ 110 mg/dl | Type 2 diabetes, impaired glucose tolerance or insulin resistance<br>➔ Lowest 25% percentile for insulin sensitivity by euglycaemic clamp or highest quartile fasting insulin or HOMA | Impaired Fasting glucose<br>100 – 126 mg/dL **OR**<br>2-hr post oral glucose (75g)<br>> 140 mg/dL | Hyperinsulinaemia – fasting insulin above the upper quartile for non-diabetic individuals<br>Impaired fasting plasma glucose ≥ 6.1 mmol/L<br>(≥ 5.6 mmol/L venous or capillary whole blood) |
| Dyslipidaemia<br>Triglycerides | ≥ 1.69 mmol/L | ≥ 1.69 mmol/L | | ≥ 2.0 mmol/L |
| HDL cholesterol | < 1.04 mmol/L (Male)<br>< 1.30 mmol/L (Female) | < 0.9 mmol/L (Male)<br>< 1.0 mmol/L (Female) | < 1.04 mmol/L (Male)<br>< 1.30 mmol/L (Female) | < 1.0 mmol/L (Male or Female) and/or treatment for dyslipidaemia |
| Blood Pressure | ≥ 130/≥85 mmHg | ≥ 140 / 90 mmHg or on antihypertensive medication | ≥ 130 / 85 mmHg | ≥ 140 / 90 mmHg and/or treatment for hypertension |
| Microalbuminuria | Not utilized for diagnosis | Urinary Albumin > 20 µg/min **OR** Alb/Cr > 30 mg/g | Not utilized for diagnosis<br><br>Other risk factors:<br>e.g. Family history of Type 2 DM, Hypertension or Cardiovascular Disease | Not utilized for diagnosis |

**AACE** = American Association of Clinical Endocrinologist (Endocr Pract. 2003: 9(3); 240 – 252), BMI = Body mass index; **EGIR** = European Group for the study of Insulin Resistance (Diabetes Metab. 2002 Nov; 28(5):364-76); **HOMA** = Homeostasis Model Assessment; **NCEP ATP III** = National Cholesterol Education Program, Adult Treatment Panel III (JAMA 2001; 285: 2486 – 2497); **WHO** = World Health Organisation. (Diabet Med 1998; 15: 539 – 553).

considerable disparity within the expert panel criteria for the individual metabolic traits, as well as the syndrome itself.

It was recognised that existing guidelines put forward by the World Health Organisation (WHO) and National Cholesterol Education Program – Third Adult Treatment Panel (NCEP ATP III) were never intended to provide exact diagnostic criteria for identifying individuals with metabolic syndrome in clinical practice. However, there is a need for a single, universally accepted diagnostic tool that is easily to apply in clinical practice. Hence, the International Diabetes Federation (IDF) held a press release in April 2005 to launch its worldwide definition of the metabolic syndrome (Table 1.2). This new definition addresses both clinical and research needs, providing an accessible, diagnostic tool suitable for worldwide use and establishing a comprehensive list of additional criteria that should be included in epidemiological studies and other research into the metabolic syndrome. Although the pathogenesis of the metabolic syndrome and each of its components is complex and not well understood, central obesity and insulin resistance are acknowledged by the IDF as important causative factors. Central obesity is most easily measured by waist circumference, which is gender and ethnic-group specific. The IDF also specifies the recommendations for these specifications in its definition.

**Table 1.2: The IDF consensus worldwide definition of the metabolic syndrome for use in clinical practice (IDF 2005)**

| | |
|---|---|
| For a person to be defined as having the metabolic syndrome, they must have: | |
| **Central obesity** | |
| • Waist circumference for Chinese | ≥ 90 cm in males<br>≥ 80 cm in females |
| **Plus any TWO of the following four factors:** | |
| • triglyceride levels **OR** specific treatment for this lipid abnormality | ≥ 1.7 mmol/L |
| • ↓ HDL-cholesterol | < 1.03 mmol/L in males<br>< 1.29 mmol/L in females |
| • ↑ blood pressure **OR** treatment of previously diagnosed hypertension | systolic BP ≥ 130 or diastolic ≥ 85 mm Hg |
| • ↑ fasting plasma glucose **OR** previously diagnosed type 2 diabetes | ≥ 5.6 mmol/L |

## 1.2 Clinical States of the metabolic syndrome

The metabolic syndrome is characterized by many metabolic abnormalities, including impaired glucose tolerance, insulin resistance, dyslipidaemia, hypertension, central obesity, coagulation anomalies favouring thrombosis, hyperuricaemia and occasionally, polycystic ovary syndrome. Together, these abnormalities create a metabolic environment that increases the risks of macrovascular atherosclerotic

abnormalities, such as stroke, heart attack, peripheral vascular disease, as well as renal failure.

### 1.2.1 Impaired glucose tolerance (IGT) and Impaired Fasting Glucose (IFG)

The expert committee on the Diagnosis and Classification of Diabetes Mellitus recognized an intermediate group of subjects whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal (Table 1.3). This group is defined as having FPG levels ≥ 5.6 mmol/L but < 7.0 mmol/L or 2-h values in the oral glucose tolerance test (OGTT) of 7.8 mmol/L but < 11.1 mmol/L (American Diabetic Association 2004).

Patients with IFG and/or IGT are now referred to as having "pre-diabetes" indicating the relatively high risk for development of diabetes in these patients.

**Table 1.3: Criteria for the diagnosis of diabetes (American Diabetes Association 2004)**

| | Normoglycaemia | IFG or IGT | Diabetes |
|---|---|---|---|
| FPG (mmol/L) | < 5.6 | ≥ 5.6 and < 7.0 (IFG) | ≥ 7.0 |
| OGTT † 2h-post glucose (mmol/L) | < 7.8 | ≥ 7.8 and < 11.1 (IGT) | ≥ 11.1 Symptoms of diabetes and RPG ≥ 11.1 mmol/L |

In the absence of unequivocal hyperglycaemia, a diagnosis of diabetes must be confirmed, on a subsequent day, by measurement of FPG, 2-h post glucose or random plasma glucose (if symptoms are present). The FPG test is greatly preferred because of ease of administration, convenience, acceptability to patients, and lower cost. Fasting is defined as no caloric intake for at least 8h.
† This test requires the use of a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

### 1.2.2 The metabolic syndrome and type 2 diabetes mellitus

It has been proposed that the metabolic syndrome is a powerful determinant of type 2 diabetes mellitus and cardiovascular disease (Reaven GM 1988 and Defronzo RA et al 1991).

The ADA defined diabetes mellitus as "a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both". Chronic hyperglycaemia of diabetes will cause long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels (Reaven GM, 1988, DeFronzo Ra 1991, UKPDS 23, 1998).

The last two decades have seen a huge global increase in the diabetic patients. Currently, it is estimated that 150 million people in the world suffering from diabetes. This number is expected to increase to 300 million by the year 2025 (Kumanyika S et al 2002). The metabolic syndrome is now recognized as an early metabolic abnormality that precedes the development of type 2 diabetes (Alberti KG et al 1998). In the FINRISK study cohort, the prevalence of the metabolic syndrome was 91.5 and 82.7% in subjects with type 2 diabetes in men and women respectively (Ilanne-Parrikka P et al 2004). Prevention of type 2 diabetes should therefore aim to prevent and treat several components of the metabolic syndrome simultaneously.

### 1.2.3 Dyslipidaemia

Both the decrease in HDL-cholesterol and increase in LDL-cholesterol are well-established risk factors for coronary artery disease (CAD) and other macrovascular complications (Castelli WP et al 1989). The characteristic lipid profile in a Type 2 DM patient includes decreased serum HDL-cholesterol, increased serum VLDL-cholesterol and an increase in triglycerides.

A close relationship between hyperinsulinaemia and hypertriglyceridaemia has been described in population-based studies in healthy normal weight subjects (Zavaroni et al 1989, Orchard TJ et al 1983). In 1991, Defronzo and Ferrannini extended the concept of hyperinsulinaemia as one of the cause of an atherogenic

plasma lipid profile. They explained that elevated plasma insulin concentrations enhance VLDL-cholesterol synthesis, leading to hypertriglyceridaemia. Progressive elimination of lipid and apolipoproteins from the VLDL particle leads to an increased formation of intermediate-density and low-density lipoprotein, both of which are atherogenic. Plasma insulin and HDL-cholesterol concentrations was inversely correlated (Orchard TJ et al 1983 and Golay A et al 1987). Therefore, hyperinsulinaemia is associated with a reduced HDL-cholesterol levels and increased risk for CAD. Consequently, it is important to recognize that insulin resistance represents the basic underlying defect in abnormal plasma lipid profile (Defronzo RA and Ferrannini E 1991).

In addition, insulin, independent of its effects on blood pressure and plasma lipids, is known to be atherogenic (Jarret RJ 1988). The hormone enhances cholesterol transport into arteriolar smooth muscle cells and increase endogenous lipid synthesis by these cells. Insulin also augments collagen synthesis in the vascular wall. Since insulin itself is a growth-promoting substance, it may bind to receptors of various other growth factors, including Insulin-like Growth Factor I (IGF-I), which cause cells to proliferate and thereby contribute to the atherosclerotic process (Sinha MK et al 1989). The major effects of insulin on arterial tissues are summarized in Table 1.4.

**Table 1.4: Effect of Insulin on arterial tissues ***

| |
|---|
| Smooth muscle cells proliferation |
| Enhanced cholesterol synthesis and LDL-receptor activity |
| Build-up if triglycerides and free fatty acids |
| Increased formation and decreased regression of lipid plaques |
| Stimulation of connective tissue synthesis |

*Adapted from DeFronzo RA and Ferrannini E 1991

### 1.2.4 Hypertension

Elevated blood pressure is included in most definitions of the metabolic syndrome, but its relation to the syndrome is complex. The mechanism and pathophysiology of hypertension are associated with the metabolic abnormalities seen in the metabolic syndrome (Table 1.5). Because of the compensatory hyperinsulinaemia caused by insulin resistance, the sympathetic nervous system is stimulated, causing vasoconstriction, increased cardiac output, and renal absorption of sodium, which in turn, leads to elevated blood pressure sufficient to override the direct normal vasodilating action of insulin in obese and hypertensive patients.

Insulin may also indirectly increase blood pressure by decreasing the signaling processes that are important for vascular relaxation (DeFronzo RA et al 1991, Cranford LS 2003). Insulin, by actions on IGF-I, may cause the hypertrophy of the vascular wall and narrowing of the lumen of the resistance vessels involved in the

regulation of systemic blood pressure, thus, contributing to the development of hypertension and atherogenesis (DeFronzo RA et al 1991).

**Table 1.5: Mechanisms by which insulin can elevate blood pressure:**

| |
|---|
| Kidney sodium retention |
| Sympathetic nervous system activation |
| Enhanced fluxes of Na+ and Ca+ into vascular smooth muscle cells, leading to an increased vascular sensitivity to the vasoconstrictor effect of pressor amines |
| Proliferation of arteriolar smooth muscle cells |

### 1.2.5 Obesity

In non-diabetic patients, excessive calories and weight gain will result in the body being markedly resistant to the action of insulin (Sims EAH et al 1973). Many investigators have shown that using the euglycaemic insulin-clamp technique, tissue sensitivity to insulin declines by approximately 30 – 40% when an individual becomes > 35 –40 % over ideal body weight (Bonadonna R et al 199 and Golay A et al 1988). Cross-sectional data (Park YW et al 2003) indicate that the dose response of body mass index versus prevalence of metabolic syndrome is sigmoidal, with a $K_m$ approximately 26 $kg/m^2$ in women and 28 $kg/m^2$ in men, which suggests a critical impact of mild degrees of overweight.

The association between obesity and type 2 diabetes mellitus is recognized for decades, since obesity is able to engender insulin resistance. Approximately 30 to 50% of obese individuals will develop diabetes mellitus or impaired glucose tolerance (Hauner H, 1999), and up to 90% of patients with type 2 diabetes mellitus are overweight or obese (Tremble JM et al. 1999). The medical consequences of obesity are well recognized and, in patients with diabetes, may contribute to other comorbidities.

The relationship between obesity and insulin resistance is seen across all ethnic groups and is evident across the full range of body weights. Large epidemiologic studies reveal that the risk for diabetes, and presumably the metabolic syndrome, rises as body fat content increases from the very lean to the very obese, implying that the "dose" of body fat has an effect on insulin sensitivity across a broad range (Colditz GA et al, 1990). Although this relationship is seen with measures of adiposity such as BMI, which reflect general adiposity, it is critical to realize that all sites of adiposity are not equal in this regard. Central (intra-abdominal) deposit of fat are much more strongly linked to insulin resistance, type 2 diabetes, and cardiovascular disease than are peripheral (gluteal/subcutaneous) fat depots. Although obesity per se is associated with increased morbidity, the association is even stronger for truncal fat and particularly visceral fat (Vague J 1956, Pi-Sunyer

FX 1993). It was also demonstrated that visceral fat accumulation is associated with dyslipidaemia, hypertension, insulin resistance and albuminuria in Chinese patients with Type 2 diabetes mellitus (Anderson PJ et al 1997). When compared with subcutaneous adipose tissue, visceral adipocytes exhibit increased sensitivity to the lipolytic effects of catecholamines and reduced sensitivity to the antilipolytic effects of insulin (Chen YDI et al, 1987). Both genetic and environmental factors contribute to the development of obesity and the distribution of body fat.

## 1.3 Effects of weight loss on the metabolic syndrome

Lifestyle modification is the cornerstone of treatment for the metabolic syndrome. Recent treatment guidelines for the metabolic syndrome have emphasized the clinical utility of diagnosis and an important treatment role for "therapeutic lifestyle change", incorporating moderate physical activity. Recent review has considered exercise training effective in the treatment of insulin resistance and related components of the syndrome. However, the evidence for exercise effects has been considered less consistent for dyslipidaemia, impaired glucose regulation and hypertension, unless exercise training is combined with appropriate dietary modifications to achieve weight loss. Thus, an effective lifestyle modification includes both diet and exercise therapy, aimed at achieving a net negative energy

balance by decreasing energy intake and increasing energy expenditure, with the goal of decreasing both body weight and insulin resistance (Miranda PJ et al 2005).

A number of clinical trials have approached the problem of reducing insulin resistance by increasing the level of physical activity, which has the potential benefits of enhancing insulin sensitivity and enabling increased weight loss. The Da Qing IGT and Diabetes Study, the Finnish Diabetes Prevention Study, and the Diabetes Prevention Program (DPP), demonstrated that modest weight loss achieved by lifestyle changes (diet and exercise) can significantly reduce the risk of developing type 2 diabetes in obese patients with IGT (Tuomilehto J et al, 2001, Knowler WC et al, 2002.). Lifestyle intervention improved CVD risk factor status in the DPP study: triglyceride levels fell significantly more with intensive lifestyle intervention while HDL-cholesterol and LDL-particle size increased significantly, sustained over the course of the study (Diabetes Prevention Program Research Group 2005). Weight reduction of 5 to 10% improves serum glucose (Wing R et al. 1994) and insulin levels (Watts NB et al. 1990). The Swedish Obese Subjects (SOS) study has demonstrated that large weight losses in obese patients are associated with an 80% reduction in the 8-year incidence of diabetes (Sjöström CD et al, 2002).

## 1.4 Ethnic differences in the prevalence of the metabolic syndrome

Since the prevalence of hypertension, insulin resistance and glucose intolerance usually increase with increasing age, the prevalence of the metabolic syndrome will probably also rise in the aging society.

According to the ATP III definition, an estimated of > 20% of American adults have the metabolic syndrome. Mexican Americans had the highest age-adjusted prevalence of 31.9%. Among African-Americans, women had about a 57% higher prevalence than men did. Using the 2000 census data, about 47 million US residents have the metabolic syndrome (Ford ES et al 2002).

In the Finnish population, using the WHO criteria for the metabolic syndrome, it is estimated that the metabolic syndrome was present in 38.8 % of men and 22.2 % of women in the FINRISK study cohort. The study also reported a prevalence of 84.8 and 65.4 % in subjects with IGT affected with the metabolic syndrome (Iilanne-Parrikka P et al 2004). In the Finnish Diabetes Prevention Study (DPS), 78.4 % of men and 72.2 % of women with IGT had the metabolic syndrome (Tuomilehto J et al 2001).

In an urban Korean population, when adopting the ATP III criteria, the prevalence of the metabolic syndrome was 16.0% in men and 10.7% n women aged 30 – 80 years. However, when the waist circumference is reduced from 102 to 90cm

in men and 88 to 87cm in women, the prevalence of the metabolic syndrome increased to 29.0 and 16.8% respectively (Oh JY, et al 2004).

## 1.5 Treatment of the metabolic syndrome

Early recognition is important to the healthcare provider as it is critical to effective, long-term, comprehensive patient management. Prevention of the metabolic syndrome and treatment of its main characteristics are now considered of utmost importance in order to combat the epidemic of type 2 diabetes mellitus and to reduce the increased risk of cardiovascular disease and all-cause mortality (Foster DW 1989).

In the ACEP III report 2001, the National Cholesterol Education Program (NCEP) Expert Panel acknowledged the metabolic syndrome as one potential secondary target of therapy. It stated that management of the metabolic syndrome has a two-fold objective including the reduction of underlying causes and treating associated nonlipid and lipid risk factors if they persist despite the recommended lifestyle therapies (Executive summary of the third report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of high blood cholesterol in adult 2001). Treatment must address the multipathologic process of the metabolic syndrome, with each component identified and aggressively targeted for treatment.

**Table 1.6: Treatment of the metabolic syndrome**

- Treat underlying causes (i.e. obesity and physical inactivity):
  - Intensifying weight management
  - Increase physical activity; and
- Treat associated nonlipid and lipid risk factor if they persist despite these lifestyle therapies:
  - Treat hypertension
  - Use aspirin for CHD patients to reduce prothrombotic state
  - Treat elevated triglycerides and/or low HDL-cholesterol

## 1.6 Oral Antidiabetic agents and their failure in the metabolic syndrome

A number of pharmacological therapies can be used for the treatment of the metabolic syndrome, but the results of most of the available therapies are often unsatisfactory.

### 1.6.1 Sulphonylureas

The sulphonylureas are very commonly used for type 2 diabetes mellitus. These have been available in the United States since 1954. Sulphonyureas binds to the sulphonylurea receptor on pancreatic β-cells. This ultimately leads to insulin secretion and hence, allow for insulin release at lower glucose thresholds than normal (Zimmerman BR. 1997). They partially reverse the attenuated insulin secretion that characterizes type 2 diabetes. Understandably, circulating insulin concentrations are

increased. As a result and despite the presence of insulin resistance, glucose concentrations fall.

Given the epidemiological association between hyperinsulinaemia and cardiovascular disease, some have raised concerns that sulphonylureas increase cardiovascular morbidity (Wilson et al 2001, Ashcroft et al 1999), which is already a great concern in the metabolic syndrome. But in the UK Prospective Diabetes Study 1998 (UK Prospective Diabetes Study Group 1998), increased mortality was not shown. Due to these agents' mechanism of action, there is a concern is their potential to exhaust β-cell function. However, as demonstrated by in the UKPDS, the inexorable decline in β-cell function may be an underlying characteristic of the diabetic state itself, independent of treatment modality. Of more practical concern, sulphonylurea therapy is associated with weight gain, especially problematic in a group of frequently overweight patients, and hypoglycaemia. Therefore, sulphonylurea therapy is not recommended in the metabolic syndrome.

### 1.6.2 Biguanides

In contrast to the sulphonylureas, metformin, the only biguanide available, does not stimulate insulin secretion (Johansen K et al. 1999). The precise mode of action of metformin remains somewhat controversial, but its predominant effect is to

reduce the hepatic glucose production in the presence of insulin (Hundal RS et al. 2000). It is therefore considered an insulin sensitiser.

Metformin monotherapy however is associated with weight loss (or no weight gain) and much less hypoglycaemia than sulphonylurea therapy (Johansen K. 1999). Over a period of years, weight gain for diabetic patients on metformin was slower than that for patients on sulphonylureas or insulin. Because of the lack of β-cell stimulation, circulating insulin concentrations tend to decline, which may provide a cardiovascular advantage. Other nonglycemia benefits included decreases in lipid levels (LDL-cholesterol and triglycerides) and antifibrinolytic factor plasminogen activator inhibitor-1.

The DPP also showed significant decreases in the rate of development of new type 2 diabetes cases, with 7.8% per year of the metformin group, which is a 31% reduction. The DPP has also demonstrated that metformin is effective at slowing metabolic deterioration in individuals with impaired glucose tolerance (Knowler et al 2002). Thus, metformin is a candidate drug for treatment of the glycaemic components of the metabolic syndrome. However, there is a need for additional therapies after several years of used as shown in the UKPDS, as β-cells failure also occurs in patients who are treated with metformin (UK Prospective Diabetes Study Group 1998).

### 1.6.3 Alpha-Glucosidase Inhibitors

These agents, represented by acarbose and miglitol, is the sole drug class not targeted at a specific pathophysiological defect of type 2 diabetes mellitus. These drugs competitively inhibit α-glucosidase at the small intestinal epithelium, hence preventing the breakdown of disaccharides and more complex carbohydrates, resulting in delay intestinal carbohydrate absorption and mitigate postprandial glucose excursions (Lebowitz HE 1998).

The α-glucosidase inhibitors has a considerably less efficacy as compared to either the sulphonylureas and metformin, exerting their greatest effect on post-pranial glucose levels. However, this effect on fasting blood glucose levels is small (Hoffman J et al 1997, Chiasson JL et al 1994). Despite that, α-glucosidase inhibitors are still attractive as they are essentially nonsystemic and not associated with hypoglycaemia and weight gain. Nonglycaemic advantages included small reductions in triglycerides and postpranial insulin levels (Scott R et al 1999).

In the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) used acarbose to test the hypothesis that this agent might prevent the development of Type 2 diabetes mellitus in individuals with metabolic syndrome and was subsequently found to work successfully. Only 32% of patients taking acarbose developed diabetes, compared with 42% randomized to placebo (Chiasson JL et al.

2002). However, there have been no studies that have examined long-term effectiveness of these agents in reducing chronic complications.

### 1.6.4 Peroxisome Proliferator-Activated receptors (PPARs)

The discovery of nuclear peroxisome proliferator-activated receptors (PPARs) and subsequent insight into their role in several metabolic pathways was a major breakthrough in our understanding of pathophysiological mechanisms underlying the metabolic syndrome (Vamecq J et al. 1999). PPARs are ligand-activated transcription factors belonging to the nuclear receptor superfamily (Lemberger T et al, 1996). As transcription factors, PPARs regulate the expression of numerous genes and affect glycaemic control, lipid metabolism, vascular tone and inflammation. In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle and liver.

Activation of PPARγ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization (Figure 1.1). In addition, PPARγ-responsive genes also participate in the regulation of fatty acid (Wilson TM et al 2000).

Three subtypes of PPARs are known: PPAR-α, PPAR-γ and PPAR-δ. PPAR-γ is found in adipose tissue, pancreas, skeletal muscle and vasculature (Loviscach M et al, 2000). Thiazolidinediones are potent synthetic ligands for PPAR-γ activation.

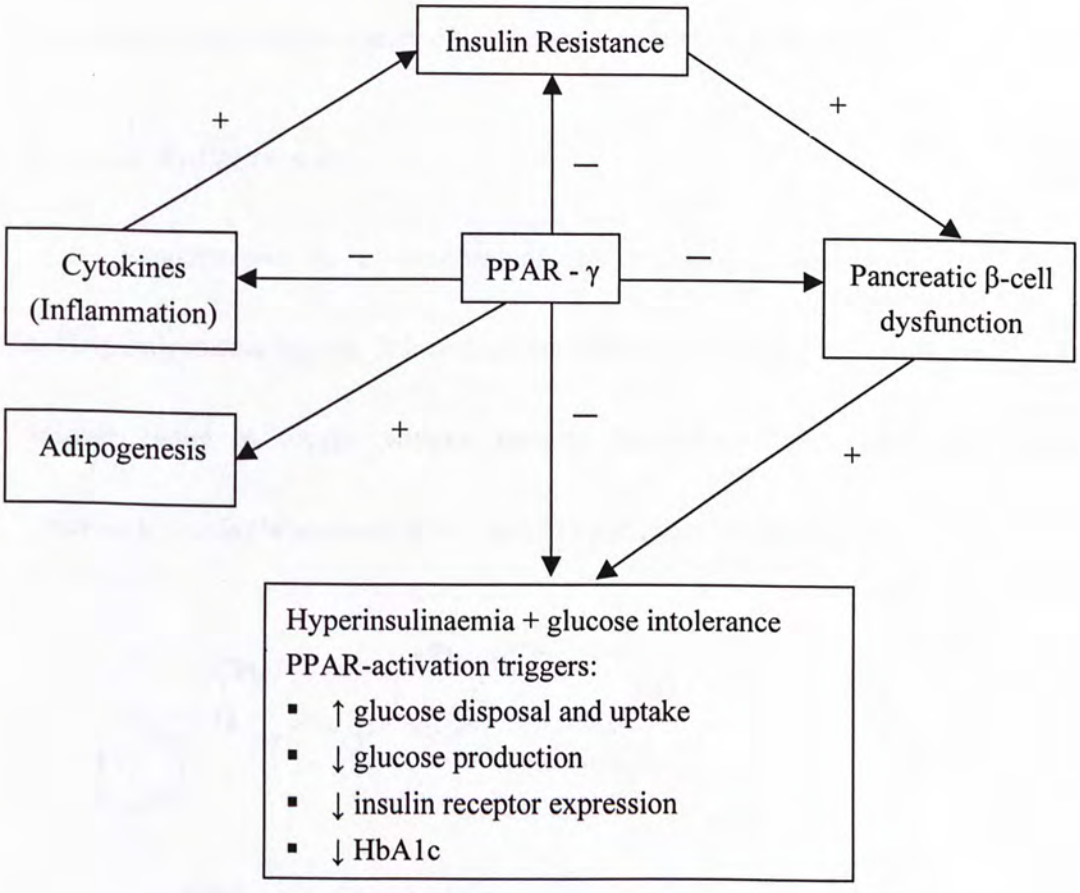
### 1.6.4.1 Thiazolidinediones

Thiazolidinediones are a new class of drugs that act primarily by improving insulin sensitivity in different target tissues such as liver, skeletal muscle and adipose tissue. They have been shown to improve glycaemic control in patients with type 2 diabetes and appear to have favourable direct effects on other components of the metabolic syndrome because of the role of PPAR-γ in vascular physiology.

Thiazolidinediones are pharmacological ligands for PPAR-γ. When activated, PPAR-γ binds with response elements on DNA, altering transcription of a variety of genes that regulate carbohydrate and lipid metabolism (Mudaliar S et al. 2001). The most prominent effect is increased insulin-stimulated glucose uptake by skeletal muscle cells. Thus, these agents decrease insulin resistance in peripheral tissues and hepatic glucose production (Petersen KF, et al. 2000).

Thiazolidinediones also have a beneficial effect on the dyslipidaemia associated with the metabolic syndrome: they decrease levels of triglycerides and free fatty acids, and they increase HDL-cholesterol levels (Komers R et al 1998). Thiazolidinediones do not lower the total LDL-cholesterol level but produce an increase in the level of large, buoyant LDL particles and a decrease in the number of small, dense LDL particles (Lebovitz HE 2002).

**Figure 1.1. The central role of peroxisome proliferator-activated receptor (PPAR)-γ in vascular physiology.**




Thiazolidinediones are chemically and functionally unrelated to other classes of oral antihyperglycaemic agents. Two compounds in this class are currently available for clinical use, namely rosiglitazone, which was approved by the United States (US) Food and Drug Administration (FDA) in May 1999, and pioglitazone, which was approved in July 1999. Troglitazone, the first thiazolidinedione, was marketed in the US from March 1997 until it was withdrawn in March 2000 because

of rare idiosyncratic hepatocellular injury (Murphy EJ et al., 2000). In Hong Kong, rosiglitazone is generally available as a prescription only item, but for pioglitazone, there is restricted access to selected government-based hospitals.

### *1.6.4.1.1 Rosiglitazone*

Rosiglitazone is a member of the thiazolidinedione group of oral antihyperglycaemic agents. It increases the sensitivity of skeletal muscle, liver and adipose tissue to insulin without directly stimulating insulin secretion from pancreatic β-cells (Whitecomb RW et al 1995 and Day C 1999).

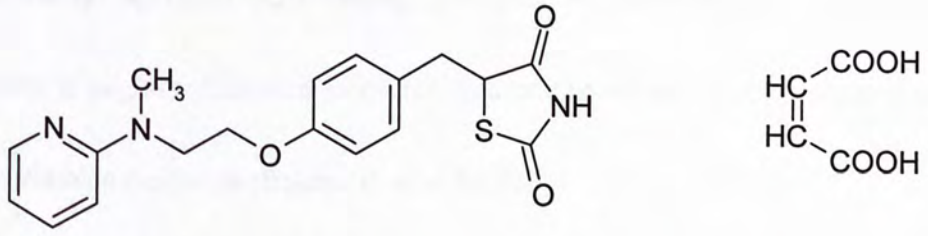



**Figure 1.2. Chemical Structure of Rosiglitazone maleate**

#### 1.6.4.1.1.1 Mode Of Action

Rosiglitazone is a highly selective and potent agonist PPAR-γ. Binding of rosiglitazone to PPAR-γ results in reduced plasma glucose levels and endogenous glucose production, and increased glucose clearance in patients with type 2 diabetes mellitus.

Rosiglitazone has several pharmacodynamic effects that could ameliorate the increased risk of cardiovascular disease in patients with the metabolic symptoms. Insulin resistance is decreased, as are plasma free fatty acids and plasma levels of small dense atherogenic LDL-C particles, despite an initial overall increase in total LDL-C. Levels of the atheroprotective large HDL particles are increased (Thomas JC et al. 2001). Changes in triglyceride levels are small and often not statistically significant (Khan MA et al. 2002, Lebovitz et al 2001).

In a clinical study reported as an abstract, diastolic blood pressure is significantly decreased (-2.3 mmHg; $p < 0.01$ vs. baseline) and systolic blood pressure is slightly decreased in 66 rosiglitazone recipients, when compared to 63 glibenclamide recipients (Bakris GL et al 2000).

While an increase in bodyweight has been associated with rosiglitazone, the increase is seen in subcutaneous fat depots rather than in visceral fat and hepatic fat depots are decreased (Carey DG et al 2000 and Banerji M et al 2001). Increases in bodyweight from baseline were similar (about 2kg) and significant ($p<0.01$) on administration of rosiglitazone for 4 months in a randomized non-blinded study of patients with type 2 diabetes mellitus (Khan MA et al. 2002).

Rosiglitazone has beneficial effects on pancreatic β-cell function in obese and non-obese patients with type 2 diabetes mellitus, suggesting possible positive effects on disease progression.

Rosiglitazone appears to be effective in patients from differing ethnic groups such as Indo-Asian, Mexican and Chinese (Barnett AH et al 2001, Gómez-Perez FJ et al 2002, Zhu X et al 2001) and in elderly patients (Beebe KL 1999).

#### 1.6.4.1.1.2 Adverse Effects & current status

Rosiglitazone is generally well tolerated. Adverse effects occurring at an incidence of ≥ 5% included upper respiratory tract infection, injury and headache. It can also cause fluid retention, in a dose-related manner (SmithKline Beecham Pharmaceuticals, Prescribing information 2001). This effect may, in part, be a result of increased insulin-stimulated vasodilatation as a consequence of increased insulin sensitivity. As with other thiazolidinediones and as seen with intensive therapy with sulphonylureas or insulin in the UKPDS study, rosiglitazone is associated with significant increases in bodyweight. However, subcutaneous fat depots appear to be targeted rather than hepatic or visceral fat depots, and waist-to-hip ratios appear largely unaffected (Carey GD et al 2000 and Banerji M et al 2001).

Oral rosiglitazone is indicated in the US and Canada for use as monotherapy in non-obese and obese type 2 diabetes, in whom diabetes not adequately controlled by diet and exercise. In Europe, it can be used as monotherapy if patients is contraindicated for or intolerant of metformin (Wagstaff et al 2002, Krentz AJ et al 2005). When used as monotherapy, the recommended starting dosage is 4mg once daily or 2mg twice daily. After 8 to 12 weeks, the dosage may be increased to 8mg/day (given in one or two daily doses) if response is inadequate. Dosage adjustments are not required for elderly patients or those with renal impairment.

## 1.7 Orlistat

Orlistat is a nonsystemically acting gastric and pancreatic lipase inhibitor that limits the absorption of dietary fat. It is a highly lipophilic hydrogenated derivative of lipastatin, a natural product of Streptomyces toxytricini (Figure 1.3).

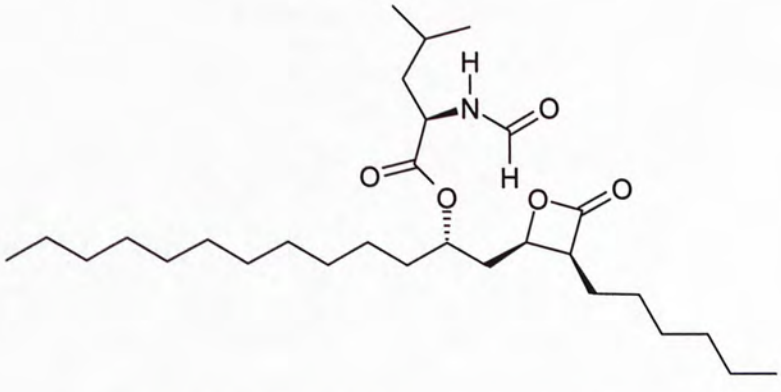



**Figure 1.3: Chemical Structure of Orlistat**

### 1.7.1 Mode Of Action

Orlistat exerts its therapeutic effect in the lumen of the stomach and small intestine. It partially prevents the hydrolysis of triacylglycerol (dietary fat) by inhibiting gastric and pancreatic lipases through the formation of a covalent bond with the active serine residue site of these enzymes. Consequently, by limiting the production of absorbable free fatty acids and monoacylglycerols, orlistat indirectly inhibits the absorption of dietary fat (Guerciolini R, 1997). Administration of orlistat 120mg with a liquid fat meal significantly reduced postpranial pancreatic lipase activity ($p < 0.03$) in the small intestine by approximately 75% by compared to placebo (Borovicka J et al 2000).

### 1.7.2 Adverse events and current status

The most frequent adverse events associated relate to the gastrointestinal system and include oily spotting, flatus with discharge, faecal urgency, fatty/oily stools, oily evacuation, increased defecation and faecal incontinence. The recommended dosage is 120 mg taken immediately before, during or up to one hour after each main meal. If a meal is missed or contains no fat, the dose should be omitted.

Orlistat is indicated in conjunction with a mildly hypocaloric diet in the treatment of obese patients with a BMI of 30 $kg/m^2$ or overweight patients (BMI of

≥ 28 kg/m$^2$) and with associated risk factors such as hypertension, diabetes or dyslipidaemia (Lucas KH et al 2001). Treatment with orlistat should only be started if diet alone has previously produced a weight loss of at least 2.5 kg over a period of 4 consecutive weeks. Treatment with orlistat should be discontinued after 12 weeks if patients have been unable to lose at least 5% of their body weight as measured at the start of drug therapy (F. Hoffmann-La Roche Ltd, Prescribing information, 2001).

### 1.7.3 Therapeutic Potential in the Metabolic Syndrome

As discussed earlier, obesity is a well recognised risk factor for type 2 diabetes and the primary treatment for type 2 diabetes is weight loss. With orlistat's unique inhibitory mode of action on the absorption of dietary fat, thereby indirectly promoting weight loss, it has a therapeutic potential in the treatment of the various aspects of the metabolic syndrome.

Orlistat use was associated with significantly improved LDL-cholesterol, total cholesterol and triglycerides. The cardiovascular risk was reduced due to a reduction in the systolic and diastolic blood pressure in addition to the lipid improvements (Hollander PA et al 1998, Hauptman J et al 2000. Rossner S et al 2000). Weight loss will also results in improved blood glucose, decreased fasting insulin concentrations and therefore, reducing insulin resistance.

## 1.8 Study Hypothesis

In view of the above mentioned pharmacology of orlistat and rosiglitazone, their use in insulin resistant patients may prove beneficial. Therefore, it was postulated that both agents, used independently, should produce some improvements in some, if not all of the parameters, of the metabolic syndrome.

## 1.9 Study Objectives

The aims of the study were :

1. to examine the effects of orlistat and rosiglitazone, in a group of Chinese patients affected by the metabolic syndrome
2. to assess the changes of cardiovascular risk factors in each groups of patients and
3. to identify the groups of patients with the best response to the therapies.

# Chapter Two

# Research Design and Methods

## 2 Study Protocol

This study was performed in accordance with the protocol as approved by the Ethics Committee of the Chinese University of Hong Kong, and in accordance with the revised Declaration of Helsinki (1983) governing experimentation with human volunteers. Patients were recruited from the Diabetes clinic of in the Prince of Wales Hospital (PWH) and all subjects gave written informed consent prior to participation. An example of the consent form is shown in Appendix I.

### 2.1 Overall Design

The study consists of a prospective, single-blinded, randomised and placebo-controlled clinical trial, which last for six months. The overall study design is shown in Table 2.1. All assessments were completed by the same members involved throughout the study (i.e. physician, certified research nurse and research student).

#### 2.1.1 Patients Selection Criteria

##### 2.1.1.1 Inclusion Criteria

Subjects of either gender between 18 to 75 years old of age and are overweight with BMI more than 23 $kg/m^2$ , diagnosed to have

## Table 2.1 : Overall design of the study

| Visit | 1<br>Run-in<br>Day 28 / - 4 weeks | 2<br>Randomisation<br>Day 0 | 3<br>On treatment<br>Week 4 (± 2 days) / 1 month | 4<br>On treatment<br>Week 12 (± 2 days) / 3 months | 5<br>On treatment<br>Week 24 (± 2 days) / 6 months |
|---|---|---|---|---|---|
| Inclusion / Exclusion Criteria | X | | | | |
| Sign, written, dated informed consent form | X | | | | |
| Female subjects – urine pregnancy test | | X | | | |
| Prior/Concomitant medication | X | X | X | X | X |
| Weight (kg) | X | X | X | X | X |
| Height (m) | X | X | X | X | X |
| Blood Pressure and heart rate | X | X | X | X | X |
| Fasting Plasma Glucose | X | X | X | X | X |
| Hb1Ac | | X | | X | X |
| Total Cholesterol | X | X | X | X | X |
| Triglyceride | X | X | X | X | X |
| HDL-cholesterol | X | X | X | X | X |
| LDL-cholesterol | X | X | X | X | X |
| Complete Blood Count | X | X | X | X | X |
| Renal/Liver Function | X | X | X | X | X |
| History | X | | | | |
| Physical Examination | | X | | | X |
| Dietary advice | X | X | X | X | X |
| Anthropometrics parameters:<br>- Mid-arm (cm), Waist (cm), Hip (cm)<br>- Skinfold thickness, subscapular, biceps, triceps, iliac | | X | X | X | X |
| OGTT: (75g oral glucose tolerance test) | | X | | | X |
| Common Carotid Arteries thickness scan<br>- Right and Left | | X | | | X |
| Dispense study medication | | X | X | X | |
| Dispense placebo | X | | | | |
| Adverse Events | | X | X | X | X |
| Drug Compliance | | X | X | X | X |

impaired glucose tolerance after repeated OGTT or type 2 diabetes mellitus with glucose intolerance controlled by diet or by only one oral hypoglycaemic agent was recruited. The criteria for IGT have been defined earlier by the American Diabetes Association (Table 1.2). Female patients of childbearing potential are eligible to enter and participate in the study if they have a negative urine pregnancy test prior to enrolment and they will practice an acceptable method of birth control during the period of study. Patients will also be assessed on their willingness and ability to comply with the study protocol, for example on the completion of provided diary cards and study drug administration, before being recruited into the trial.

#### 2.1.1.2 Exclusion Criteria

Female subjects who are pregnant or breast-feeding or planning a pregnancy during the course of the study or who are of child-bearing potential and not using an accepted method of birth control were excluded from the study. This is because the effect of study medications on pregnancy is unknown. Also excluded are patients on insulin or more than one oral hypoglycaemic agents, patients taking appetite suppressant drugs on a regular basis (including herbals and nutritional supplements for weight loss or control purposes) and patients with known hypersensitivity to any of the study medications. Other exclusion conditions included documented coronary

artery disease or pancreatic disease; any history or presence of cancer, psychiatric or neurological disorders requiring chronic medications that may influence compliance of study medication; history of alcohol or substance abuse, and impaired hepatic or renal function (AST, ALT >1.5 times the upper limit of normal, serum creatinine >115 μmol/L). In addition, patients that are currently enrolled or have participated in other clinical trials within 30 days prior to the screening visit are not eligible for the study.

### 2.1.2 Recruitment Period

#### 2.1.2.1 Screening Period

Patients were screened for eligibility according to the inclusion and exclusion criteria described earlier during their regular visit to the Prince of Wales Hospital Diabetes Specialty Clinic. If the patient met the entry criteria and had agreed to participate in the study, he would be referred to the certified research nurse, who would then give a full verbal and written explanation of the study protocol (Appendix II). Visit 1 appointment was then given to the patient at the Clinical Pharmacology Studies Unit and the patient referred to a dietitian for assessment of his daily energy requirement. A balanced hypocaloric diet, targeting an energy deficit of 500 kcal to 800 kcal below enrollment weight maintenance requirements, was

provided to each of the subjects. The subjects were then counseled to maintain the hypocaloric diet and usual exercise regimen (at least a 30 minute aerobic exercise daily) during the run-in period and study period.

#### 2.1.2.2 Run- In Period (Visit 0)

During Visit 0, a consent form in Chinese (Appendix I) was then given to the patient to be signed. Subjects then undergo routine investigations as detailed in Table 2.1 and their full medical or surgical history taken.

Medications in the form of capsules, were packed into three different containers, each labeled for breakfast, lunch or dinner. Patients were instructed to take a capsule immediately before or after each main meal as according to the containers. Should the patient forget to take the study medication and it is past an hour after the meal, patients were told to forgo that dose and indicate the reason in the medication diary. During this run-in period, a 4-weeks supply of placebo was given and patients who demonstrated to have at least 70% compliance with the placebo during the run-in period will enter the randomised treatment period. Patients were instructed to bring all study medications (including empty bottles) to each study visit and appointment for Visit 1 was made.

### 2.1.2.3 Randomisation

At the end of the initial assessment period at Visit 0, a pill-count and medication diary was used to assess the compliance of patients and incidence of adverse events. Non-compliance is defined as study medication consumption of less than 70%. Following review of the laboratory results, those compliant subjects who still fulfilled the inclusion criteria then undergo physical examination by the physician and details of prior and concomitant medications were recorded. A standard 75 g OGTT was given with blood samples drawn on 0 minute, 30 minute, 60 minute and 120 minute for plasma glucose and insulin levels. An ultrasound examination of the wall thickness of the left and right common carotid arteries was performed. The clinical record form (CRF) was completed (Appendix III) and patients were randomized to one of the three treatment groups and the relevant study medications dispensed. Details regarding the taking of medications and adherence to lifestyle modifications were emphasized again.

In the orlistat group, patients were randomized to receive 120 mg of orlistat three times daily. For the rosiglitazone group, patients were given 2 mg of rosiglitazone in the morning and evening doses, the afternoon dose was substituted with lactose-filled placebo. The placebo group patients received placebo for all the three doses. Hence, all patients received three different bottles of medications, each

bottle with instructions labeled to take the medications after breakfast, lunch or dinner respectively. Patients were instructed not to mix the contents of any bottles and to bring back each container as it is during the next visit.

#### 2.1.2.4 Evaluation Periods (Visit 2 to 4)

Following randomization to either of the three groups, all patients were reviewed for adverse events and routine investigations were conducted during each follow-up (Table 2.1). At the end of the study (Visit 4), an ultrasound examination of the wall thickness of the left and right common carotid arteries and a standard 75g OGTT were conducted again. The subjects were then encouraged to continue to maintain the hypocaloric diet even after the study has completed.

## 2.2 Investigations

Baseline investigations included fasting plasma glucose, glycosylated haemoglobin (Hb1Ac), lipid profiles (total cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol), renal function tests, liver functions and complete blood count. These laboratory tests were performed by the Department of Chemical Pathology at the Prince of Wales Hospital. Blood pressure and anthropometric parameters were also recorded. Additional investigations conducted at Visit 1 and

Visit 4 included a standard 75g OGTT and an ultrasound of the wall thickness of the left and right common carotid arteries conducted by the Department of Radiology, Prince of Wales Hospital. Patients were instructed not to take any medications (including oral anti-diabetic medications) prior to OGTT.

### 2.2.1 Oral Glucose Tolerance Test (OGTT)

The oral glucose test was developed by Yalow and Berson in 1960 (Yalow et al., 1960). It is the most commonly used method to evaluate whole body glucose tolerance in vivo. The procedure involves the measurement of plasma glucose and insulin at the 0-minute, 30-minute, 60-minute and 120-minute intervals following a standard 75g glucose load. It is general practice that plasma insulin levels of the corresponding plasma glucose values are also measured as they can provide additional information. Methods of assessment include calculating the plasma glucose to plasma insulin ratio (Yalow et al 1960), and more often, calculating the areas-under-the-curve (AUC) of the glucose and insulin concentrations versus time curves.

### 2.2.2 Anthropometric measurements

Recruited patients would be weight and his height measured for the determination of the BMI, which was calculated from the subject's weight and height using the formula:

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Height}^2 (\text{m}^2)}$$

A skin-caliper (Skyndex Electronic Body Fat Calculator, Justic & Co., Inc., AR, U.S.A) was used to assess the body fat. The biceps, triceps, subscapular and iliac areas were selected for measurement. Skinfold thickness measurement was obtained by pinching the skin and adjacent subcutaneous tissue between the thumb and forefinger, pulling it away from the body just far enough to allow the jaws of the caliper to impinge on the skin. The readings were repeated three times to improve accuracy and reproducibility of the measurements. The data were automatically recorded by the caliper and processed by a built-in calculator according to the formula developed by Durnin and Womersley (Durnin *et al.*, 1974):

$$\%Fat = \frac{495}{BodyDensity} - 450$$

where body density is estimated using skinfold data obtained from specific parts of the human body.

## 2.3 Analytical Methods

### 2.3.1 Determinations of insulin levels in plasma samples

Insulin levels in plasma samples were determined using the DAKO Insulin kit (DakoCytomation Ltd., 2002). The standard assay procedure and the technical

precautions are as described in the user's manual. Blood samples are collected in 5-mL specimen tubes containing heparin. Samples are centrifuged immediately at 3000 rpm for 10 minutes (Accuspin FR, Beckman, Califonia, U.S.A.) to separate plasma from blood cells. The separated plasma is then stored at –20 °C for up to 28 days.

#### 2.3.1.1 Principle of the insulin assay

Dako insulin is an enzyme linked immunosorbent assay (ELISA) for the quantitative measurement of insulin in human serum and plasma. It is based on two monoclonal antibodies. A complex is formed with the simultaneous incubation of samples and enzyme-labelled antibody in a microplate well coated with a specific anti-insulin antibody. The unbound enzyme-labelled antibody is then removed by a simple washing step. The bound conjugate is detected by reaction with the substrate 3,3',5,5'-tetramethylbenzidine. The reaction is stopped by adding acid, resulting in a colorimetric endpoint that is read spectrophotometrically at 450 nm. The assay includes a set of calibrators of known insulin concentration where a calibration curve was constructed (Figure 2.1). The level of insulin in patient samples is then calculated from the calibration curve. The assay principle is shown in Figure 2.2. The intra-assay precision had a coefficient of variation in the range of 5.1 – 7.5% and the coefficient of variation for inter-assay precision was 4.2 – 9.3% (DAKO Diagnostic Ltd., 2002).

**Figure 2.1. Calibration curve**

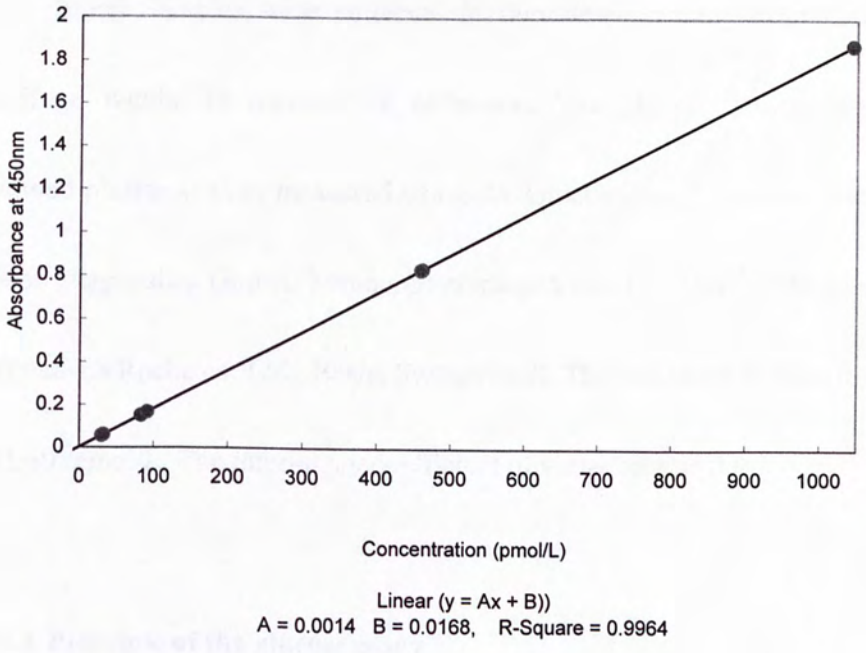
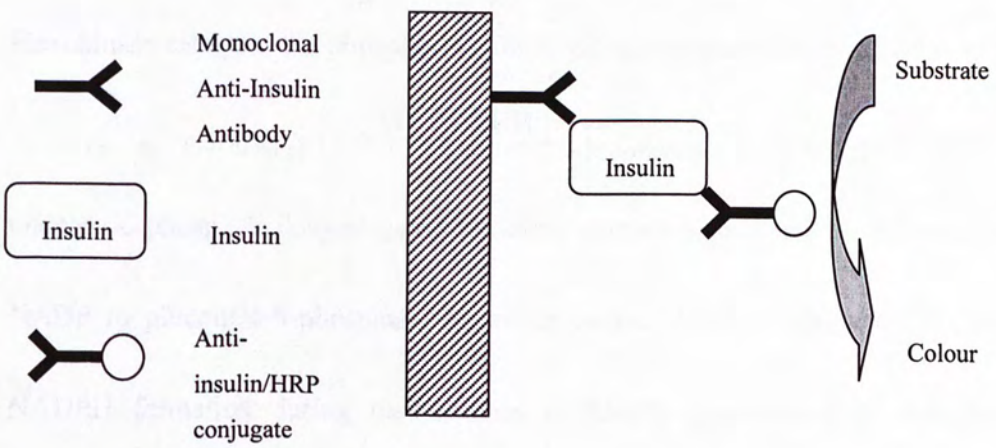



**Figure 2.2. DAKO Insulin Assay Principle**



### 2.3.2 Determination of glucose concentrations in samples

Blood Samples were collected in fluoride-containing specimen tubes and centrifuge within 30 minutes of collection. The glucose concentration in the separated plasma is then measured using the Gluco-quant ® Glucose (HK) Reagent (Roche Diagnostics GmbH, Manneim) employed in a COBAS ® MIRA analyzer (F. Hoffman-La Roche co. Ltd., Basle, Switzerland). The test range is from 0.11 mmol/L to 41.60 mmol/L. The inter-assay coefficient of variation was 0.8%.

#### 2.3.2.1 Principle of the glucose assay

The hexokinase method (Schmidt 1961, Peterson & Young 1958) is a recognized reference method. The reaction is started when the sample is added to the working reagent (buffer/ATP/NADP/Hexokinase/G-6PDH):

$$\text{glucose} + \text{ATP} \xrightarrow{\text{hexokinase}} \text{G} - 6 - \text{P} + \text{ADP}$$

Hexokinase catalyses the phosphorylation of glucose to glucose-6-phosphate by ATP.

$$\text{G} - 6 - \text{P} + \text{NADP}^{+} \xrightarrow{\text{G} - 6 - \text{PDH}} \text{gluconate} - 6 - \text{P} + \text{NADPH} + \text{H}^{+}$$

Glucose-6-phosphate dehydrogenase oxidizes glucose-6-phosphate in the presence of NADP to gluconate-6-phosphate. No other carbohydrate is oxidized. The rate of NADPH formation during the reaction is directly proportional to the glucose concentration and can be measured photometrically at 340nm.

## 2.4 Calculations

### 2.4.1 Insulin (hepatic) sensitivity (HOMA)

Many attempts have been made to assess insulin sensitivity from OGTT. Matthews and colleagues proposed the homeostatic model assessment (HOMA) to provide equations for estimating insulin resistance (HOMA-IR) and β-cell function (HOMA estimate of β-cell) from simultaneous fasting measures of insulin and glucose levels. These authors found that the HOMA-based insulin resistance (HOMA-IR) score was strongly correlated with insulin sensitivity assessed by the glucose clamp technique in both non-diabetic and diabetic subjects (r = - 0.83 and - 0.92, respectively. This approach, which relies on the product of fasting plasma glucose (FPG) and fasting plasma insulin (FPI) concentrations, has been evaluated in several publications (Philips D et al 1994, Bonora E et al 2000). In this study, HOMA refers to HOMA-IR, and it was calculated with the formula :

[Fasting plasma insulin (μU/mL) x Fasting plasma glucose (mmol/L)] / 22.5

With such a method, high HOMA scores denote low insulin sensitivity (insulin resistance). The CVs of HOMA scores as validated by Bonora E and coworkers were 9.4 ± 0.7 and 7.8 ± 0.6% respectively, in 20 non-diabetic subjects and 20 diabetic individuals.

### 2.4.2 Area Under the Curves

According to Walker EA, 1994, the measure for area under the curve is used when an integrated assessment is more useful in understanding a phenomenon. In the OGTT tests, the integrated expression of glucose and insulin levels over time may give the best assessments of the degree of increase in glucose or insulin levels. The area under the curve is a useful summary approach as it allows the use of standard methods to analysis repeated measures (Matthews JNS et al 1990). The product of the glucose area under the plasma glucose curve and insulin area under the plasma insulin curve is calculated using the trapezium rule. This rule involves the addition of the areas under the graph between each pair of consecutive observations. At measurements y1 and y2 at times t1 and t2, the area under the curve between those two times is the product of the time difference and the average of the two measurements. Thus, we get

$$\frac{(t2-t1)(y1+y2)}{2}$$

The trapezium rule can be summarized as follows:

$$AUC = \frac{1}{2}\sum_{i=0}^{n-1}(t_{i+1}-t_i)(y_i+y_{i+1})$$

### 2.4.3 Sample Size Calculations

The equation used to calculate sample size is :

$$N = \frac{(Z\alpha)^2 \times 2 \times (s)^2}{(\bar{d})^2}$$

where $Z\alpha = 1.96$, $\bar{d}$ is the mean difference that was observed, $s^2$ is the variance. In order to reduce the effect of beta error due to small sample size, a beta error of 20% (one-tailed test), which correspond to $Z\beta$ of 0.84 is used in addition to the alpha error. Therefore, the equation for sample size calculation used for this study is :

$$N = \frac{(Z\alpha + Z\beta)^2 \times 2 \times (s)^2}{(\bar{d})^2}$$

The desired statistical power is 0.95.

Considering the effects of orlistat and rosiglitazone on fasting serum glucose and insulin levels in the previous studies:

The mean FPG of orlistat-treated patients was reduced from baseline by 0.42 ± 0.05 mmol/L (Heymsfield et al 2000). The sample size needed to achieve a 95% confidence interval of ± 0.05 is $(1.96 + 0.84)^2$ x 2 x $(0.05)^2$ / $0.05^2$ = 15.68.

The mean fasting serum insulin of orlistat-treated patients was reduced from baseline by 14 ± 7 pmol/L (Heymsfield et al 2000). The sample size needed to achieve a 95% confidence interval of ± 10 is $(1.96 + 0.84)^2$ x 2 x $(7)^2$ / $10^2$ = 7.68. Based on the above estimations, the orlistat group should have a minimum of 16 patients.

The mean FPG of rosiglitazone-treated patients was reduced by 0.9 ± 2.1 mmol/L (Nolan JJ et al 2000) in the 4-mg rosiglitazone group. The sample size needed to achieve a 95% confidence interval of ± 2 is $(1.96 + 0.84)^2 \times 2 \times (2.21)^2 / 2^2 = 7.68$. Considering the 4mg rosiglitazone group, the mean insulin of rosiglitazone-treated patients was reduced from baseline by 21 ± 39 pmol/L (Nolan JJ et al 2000). The sample size needed to achieve a 95% confidence interval of ± 40 is $(1.96 + 0.84)^2 \times 2 \times (39)^2 / 40^2 = 14.9$. The rosiglitazone group should have a minimum of 15 patients. To make any comparisons meaningful in this study, it is decided that at least 16 patients should be included in each study group.

## 2.5 Statistical Analysis

All statistical analyses were performed using Microsoft Excel and Statistical Package for Social Sciences for Windows version 11.5 (SPSS, Inc.). Distributions were tested for normality using the Shapiro-Wilk W test. One-way analysis of variance (ANOVA) was used to determine if the subjects in all three groups were comparable at entry. For data not following a normal distribution, their comparability at entry were validated using a non-parametric test (Kruskal-Wallis Test).

Using laboratory data as a dependent variable, a repeated measurement analysis of variable (ANOVA) was performed to test for differences between the

three groups and between visits. To compare the different treatments with the control, the one-way ANOVA with the post hoc, Dunnett t (2-sided) test, was conducted on the percentage differences of the pre- and post-treatment of parameters. The results were expressed as mean ± SD. Non-normally distributed data were logarithmically transformed to approximate a linear distribution. Data not following a normal distribution even after transformation were validated using a non-parametric test (Kruskal-Wallis Test). Mann-Whitney U test was also used to compare the effects of different treatments with the control group.

Graphs were plotted using Microsoft Excel 2000 for Windows. A p-value < 0.05 was considered statistically significant for all data.

# Chapter Three

# Results

## 3.1. Study Population

A total of 90 potential Chinese patients age ≥ 20 years were screened but only 63 patients with persistent fasting plasma glucose ≥ 5.6 mmol/L or OGTT 2h-post glucose levels of ≥ 11.1 mmol/L were eligible and randomized into the three different study group. Five randomized patients did not complete the study, four of them refused participation study in the midst of the trial due to social or personal reasons, the most common reason cited was the inability to comply with the visits. The other patient from the control group developed a generalized allergic skin reaction to the placebo capsules shortly after randomization and hence, she could not complete the study. Therefore, a total of 58 patients were randomized and completed the study over the period of six months. The clinical characteristics of these patients were described in Table 3.1 with the diagnosis of IGT and type 2 diabetes mellitus were defined by ADA (Table 1.3) and the criteria of the metabolic syndrome employed was stated by IDF (Table 1.2). A total of 9 patients were on one anti-diabetic medication, namely metformin, glibenclamide and glipizide. 37 patients were classified as having the metabolic syndrome while 29 patients were diagnosed as having type 2 diabetes and 20 patients were diagnosed as having IGT.

**Table 3.1. Clinical characteristics of recruited patients at baseline.**

| | Orlistat | Rosiglitazone | Placebo | N (%) |
|---|---|---|---|---|
| Metabolic syndrome | 13 | 11 | 13 | 63.8 |
| Type 2 DM after OGTT not on any anti-diabetic agent | 11 | 10 | 8 | 50 |
| Type 2 DM taking one anti-diabetic agent | 3 | 4 | 2 | 15.5 |
| IGT not on any anti-diabetic agent | 5 | 6 | 9 | 34.5 |

Definition of the metabolic syndrome was defined by IDF (Table 1.2) and type 2 diabetes mellitus and IGT were defined by ADA 2004 (Table 1.3)

## 3.2. Randomization

19 patients were randomized to receive orlistat therapy, 20 patients were in the rosiglitazone group, and 19 patients recruited in the control group. Comparison of the baseline characteristics of the randomized subjects is summarized in Table 3.2, 3.3, and 3.4. In general, subjects randomized to the rosiglitazone group were slightly lighter (body weight 69.9 ± 12.5 kg) and shorter (body height 156.5 ± 7.6 cm) with a higher Hb1Ac and FPG. The orlistat group has the highest total cholesterol levels and HOMA score amongst the three groups. The control group has a higher systolic and diastolic blood pressure and a lower FPG. Interesting, the 75g OGTT 2 hour glucose and $Glucose_{AUC}$ for the control group were also less than the active treatment

groups. However, these differences were not statistically significant. The only significant difference found at baseline is the lower triglyceride levels in the control group.

## 3.3. STUDY RESULTS

The clinical characteristics of the patients were summarized in Table 3.5. At baseline, no patients were classified as normoglycaemia after 75g-OGTT. However, at the end of the six months treatment, a total of 11 patients became normoglycaemic, with 6 of them belonging to the rosiglitazone group. Also, the number of patients who were type 2 diabetes after OGTT increased while those who became IGT decreased in all three groups. Surprisingly, while the number of patients who were diagnosed with the metabolic syndrome decreased in the orlistat group, the figures increased in the rosiglitazone and control groups.

**Table 3.2 Comparison of baseline clinical characteristics of study subjects**

| CHARACTERISTICS | Orlistat | Rosiglitazone | Placebo | P-value |
|---|---|---|---|---|
| N | 19 | 20 | 19 | |
| Gender (M/F) | 11 / 8 | 9 / 11 | 7 / 12 | 0.437 |
| Age | 51.3 ± 8.4 | 49.9 ± 7.5 | 49.9 ± 10.3 | 0.860 |
| Weight (kg) | 73.3 ± 15.5 | 69.9 ± 12.5 | 75.1 ± 14.5 | 0.550 |
| Height (cm) | 161.9 ± 8.2 | 156.5 ± 7.6 | 161.2 ± 8.6 | 0.152 |
| BMI ($kg/m^2$) | 27.9 ± 4.7 | 28.3 ± 3.9 | 29.1 ± 4.6 | 0.653 |
| Waist circumference (cm) | 91.9 ± 11.9 | 90.5 ± 9.9 | 91.9 ± 8.9 | 0.847 |
| Hip (cm) | 99.0 ± 7.7 | 99.7 ± 7.3 | 103.0 ± 9.9 | 0.274 |
| Body Fat (%) | 36.6 ± 4.9 | 37.2 ± 5.2 | 38.2 ± 5.4 | 0.597 |
| Systolic BP (mmHg) | 132.2 ± 16.2 | 132.8 ± 13.6 | 141.6 ± 12.7 | 0.280 |
| Diastolic BP (mmHg) | 78.4 ± 10.5 | 75.2 ± 9.6 | 83.8 ± 10.8 | 0.119 |

Data are shown as mean ± SD

**Table 3.3: Comparison of baseline glycaemic indices of study subjects**

| CHARACTERISTICS | Orlistat ( n = 19 ) | Rosiglitazone ( n = 20 ) | Placebo ( n = 19 ) | P-value |
|---|---|---|---|---|
| $HbA_{1C}$ | 6.28 ± 0.7 | 6.6 ± 0.8 | 6.1 ± 0.6 | 0.176 |
| FPG (mmol/L) | 6.63 ± 0.89 | 6.89 ± 0.98 | 6.49 ± 0.87 | 0.293 |
| 75 g OGTT | | | | |
| • 2-hr glucose (mmol/L) | 12.72 ± 2.47 | 12.80 ± 3.56 | 11.10 ± 1.86 | 0.116 |
| • AUC Glucose (mmol/L · min) † | 1423.50 ± 231.60 | 1429.65 ± 520.35 | 1285.73 ± 190.24 | 0.360 |
| Fasting Insulin (pmol/L) †* | 94.42 ± 123.89 | 95.15 ± 87.46 | 86.48 ± 107.52 | 0.433 |
| 75 g OGTT | | | | |
| • 2-hr insulin (pmol/L) †* | 753.27 ± 844.94 | 625.66 ± 430.14 | 723.25 ± 734.59 | 0.355 |
| • AUC Insulin (pmol/L · min) †* | 58660.22 ± 57791.6 | 64657.27 ± 38340.0 | 61863.89 ± 41726.5 | 0.877 |
| HOMA †* | 4.76 ± 6.82 | 4.88 ± 4.95 | 4.23 ± 5.61 | 0.565 |

Data are shown as mean ± SD except for † data shown as median ± Interquartile Range, * Data analysed using nonparametric analysis.

**Table 3.4. Comparison of baseline lipid profiles and common carotid arteries thickness of study subjects**

| CHARACTERISTICS | Orlistat ( n = 19 ) | Rosiglitazone ( n = 20 ) | Placebo ( n = 19 ) | P-value |
|---|---|---|---|---|
| Total Cholesterol (mmol/L) | 5.24 ± 0.99 | 5.18 ± 0.69 | 4.99 ± 0.73 | 0.664 |
| Triglyceride (mmol/L) † * | 2.34 ± 2.02 | 2.03 ± 1.31 | 1.28 ± 1.31 | 0.021 |
| HDL-cholesterol (mmol/L) * | 1.36 ± 0.39 | 1.41 ± 0.31 | 1.37 ± 0.43 | 0.693 |
| LDL-cholesterol (mmol/L) * | 2.90 ± 0.93 | 2.78 ± 0.82 | 2.90 ± 0.53 | 0.881 |
| RCCA | | | | |
| • Proximal (mm) | 0.633 ± 0.14 | 0.702 ± 0.20 | 0.695 ± 0.12 | 0.331 |
| • Mid (mm) | 0.634 ± 0.17 | 0.693 ± 0.31 | 0.633 ± 0.11 | 0.997 |
| • Distal (mm) | 0.885 ± 0.27 | 0.786 ± 0.24 | 0.921 ± 0.69 | 0.527 |
| LCCA | | | | |
| • Proximal (mm) | 0.738 ± 0.21 | 0.740 ± 0.23 | 0.661 ± 0.16 | 0.342 |
| • Mid (mm) | 0.789 ± 0.27 | 0.782 ± 0.29 | 0.677 ± 0.15 | 0.466 |
| • Distal (mm) | 0.859 ± 0.21 | 0.870 ± 0.35 | 0.864 ± 0.28 | 0.941 |

Data are shown as mean ± SD except for † data shown as median ± interquartile range, * Data analysed using nonparametric analysis.

**Table 3.5. Clinical characteristics of recruited patients at the end of therapy.**

| | Orlistat | Rosiglitazone | Placebo | N (%) |
|---|---|---|---|---|
| Metabolic syndrome | 9 | 14 | 15 | 65.5 |
| Type 2 DM after OGTT not on any anti-diabetic agent | 7 | 4 | 9 | 34.5 |
| Type 2 DM taking one anti-diabetic agent | 3 | 4 | 2 | 15.5 |
| IGT not on any anti-diabetic agent | 8 | 6 | 4 | 31 |
| Normoglycaemia | 1 | 6 | 4 | 19 |

Definition of the metabolic syndrome was defined by IDF (Table 1.2) and type 2 diabetes mellitus and IGT were defined by ADA 2004 (Table 1.3)

### 3.3.1. Indices of Glycaemic Control

#### 3.3.1.1. HbA1c

There is no statistically significant difference when comparing the effects of drug treatments on HbA1c. As shown in the time plot (Figure 3.1), the control group has almost no change in the HbA1c levels at the end of the treatment. However, when compared with control, rosiglitazone has the most reduction in HbA1c with a mean difference of -0.2044 ± 0.25 mmol/L ($p = 0.64$), whereas orlistat has a mean difference of 0.111 ± 0.24 mmol/L ($p = 0.86$). Interestingly, both the rosiglitazone and orlistat group showed maximum reduction in HbA1c after 3 months of treatment, beyond which there is a rebound increase at the end of the 6 months treatment.

**Table 3.6: Comparison of the glycaemic indices of study subjects at the end of the study.**

| CHARACTERISTICS | Orlistat ( n = 19 ) | Rosiglitazone ( n = 20 ) | Placebo ( n = 19 ) | P-value |
|---|---|---|---|---|
| $HbA_{1C}$ | | | | |
| End of therapy | 6.01 ± 0.72 | 6.20 +- 0.77 | 6.22 ± 0.68 | |
| change from baseline (%) | -3.96 ± 0.08 | -4.19 ± 0.09 | 1.62 ± 0.06 | 0.075 |
| FPG | | | | |
| End of therapy | 6.23 ± 1.11 | 6.47 ± 1.18 | 6.44 ± 0.79 | |
| change from baseline (%) | -5.35 ± 0.15 | -6.11 ± 0.13 ‡ | -0.28 ± 0.13 | 0.361 |
| 75 g OGTT | | | | |
| • 2-hr glucose * | | | | |
| End of therapy | 12.25 ± 4.74 | 10.29 ± 5.2 | 11.09 ± 3.92 | |
| change from baseline (%) | -1.76 ± 0.38 | -20.74 ± 0.30 ‡ | -0.91 ± 0.34 | 0.057 |
| • AUC Glucose * | | | | |
| End of therapy | 1311.90 (1177.43 – 1460.40) | 1178.33 (1072.76 – 1447.84) | 1345.20 (1078.50 – 1563.83) | |
| change from baseline (%) | -4.84 ± 0.20 | -8.82 ± 0.25 | -5.18 ± 0.23 | 0.752 |
| Fasting Insulin * | | | | |
| End of therapy | 88.39 (48.26 – 178.24) | 61.43 (44.97 – 108.76) | 89.80 (60.31 – 252.19) | |
| change from baseline (%) | -54.45 ± 2.17 | -17.06 ± 0.77 ‡ | -58.39 ± 1.19 | 0.006 |

| CHARACTERISTICS | Orlistat ( n = 19 ) | Rosiglitazone ( n = 20 ) | Placebo ( n = 19 ) | P-value |
|---|---|---|---|---|
| 75 g OGTT | | | | |
| • 2-hr insulin * | | | | |
| End of therapy | 554.68 (430.74 – 1255.09) | 302.59 (193.08 – 487.72) | 655.72 (426.00 – 947.39) | |
| change from baseline (%) | -6.13 ± 0.33 | -23.46 ± 0.60 ‡ | -6.54 ± 0.66 | 0.067 |
| • AUC insulin * | | | | |
| End of therapy | 50161.34 (33761.12 – 88162.00) | 36412.66 (22101.53 – 49684.36) | 62939.61 (46417.79 – 73653.58) | |
| change from baseline (%) | -0.91 ± 0.30 | -28.58 ± 0.30 ‡ | -8.11 ± 0.35 | 0.005 |
| HOMA * | | | | |
| End of therapy | 4.45 (2.18 – 8.79) | 2.66 (1.35 – 5.58) | 4.15 (2.73 – 14.07) | |
| change from baseline (%) | -8.59 ± 0.54 ‡ | -19.81 ± 0.74 ‡ | -58.76 ± 1.26 ‡ | 0.006 |

Data are shown as mean ± SD or median (interquartile range), * Data analysed using Kruskal-Wallis Test.

‡ $p < 0.05$ for within groups comparison pre and post treatments.

**Figure 3.1: $HbA_{1C}$**

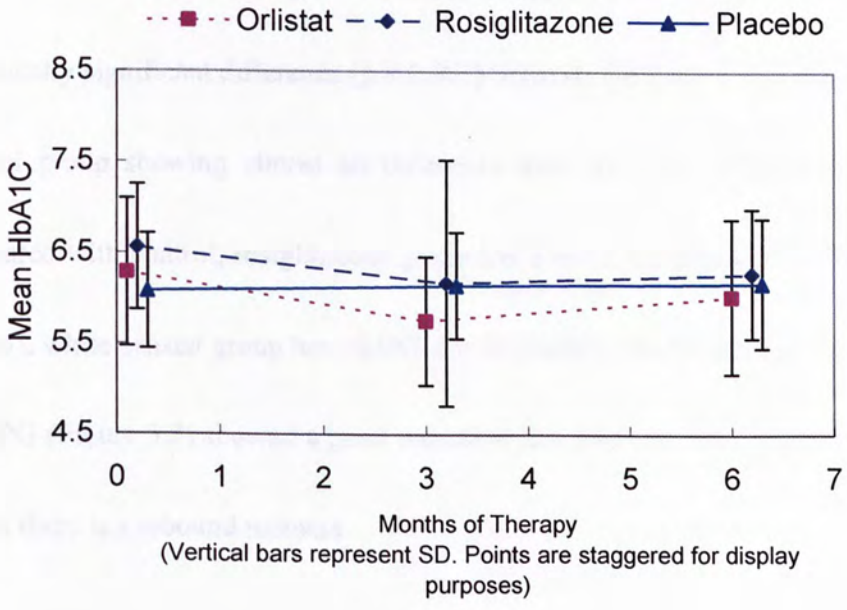
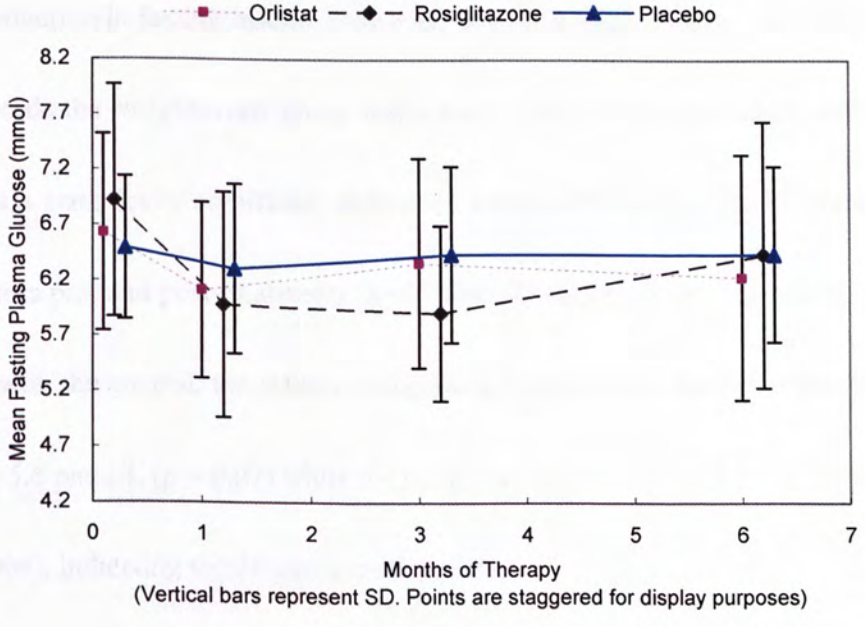



**Figure 3.2: Mean Fasting Plasma Glucose**



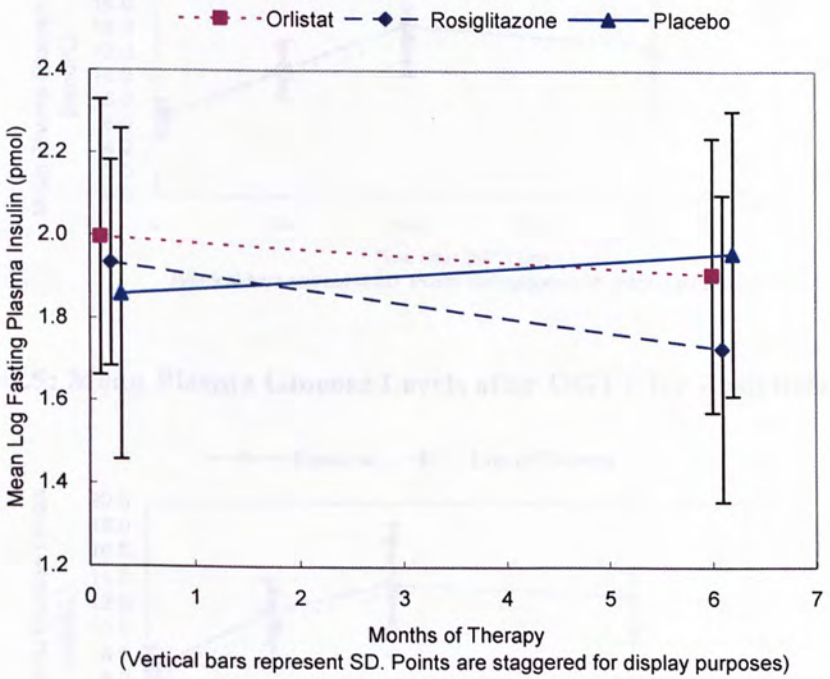
### 3.3.1.2. Fasting Plasma Glucose

There is a significant treatment effect, indicating that the treatments do reduce the fasting plasma glucose over time ($p = 0.01$). However, there is no statistically significant difference ($p = 0.903$) between the treatment groups, with the control group showing almost no difference after treatment (Figure 3.2). When compared with control, rosiglitazone group has a mean difference of $-0.109 \pm 0.25$ mmol/L while orlistat group has $-0.087 \pm 0.25$ mmol/L. As for $HbA_{1C}$, the time plot for FPG (Figure 3.2) showed a great reduction just after the start of treatment, after which there is a rebound increase.

### 3.3.1.3. Fasting Insulin

Figure 3.3 showed an interesting trend, with the orlistat group displaying a slight reduction in fasting insulin. However, there is a slight increase for the control group while the rosiglitazone group had a drop in the fasting plasma insulin value. There is a statistically significant difference amongst the groups in the percentage differences pre- and post-treatments ($p = 0.006$). When comparing the two treatment groups with the control, the orlistat group has a mean plasma insulin difference of $-11.82 \pm 5.6$ pmol/L ($p = 0.07$) while the rosiglitazone group is $-18.11 \pm 5.6$ pmol/L ($p = 0.004$), indicating significant improvements.

**Figure 3.3: Fasting Plasma Insulin**




### 3.3.1.4. 75g Oral Glucose Tolerance Test

#### 3.3.1.4.1. Glucose

The time plot (Figures 3.4, 3.5 and 3.6) for insulin levels after 75g OGTT showed that the plasma glucose levels during OGTT for the three groups were just comparable at baseline ($p = 0.058$). However, after six months of treatment, there is no apparent difference in the plasma glucose between the groups ($p = 0.539$).

**Figure 3.4: Mean Plasma Glucose Levels after OGTT for Orlistat**

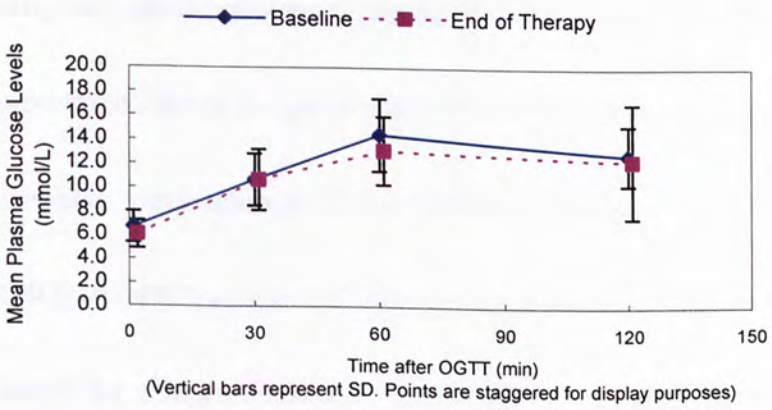



**Figure 3.5: Mean Plasma Glucose Levels after OGTT for Rosiglitazone**

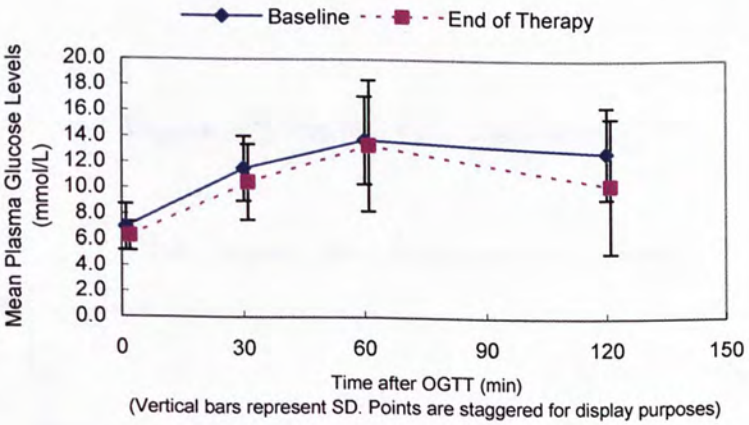
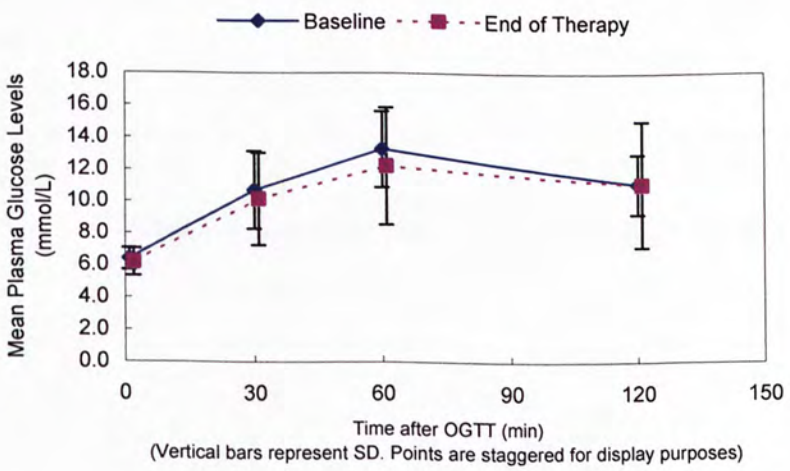


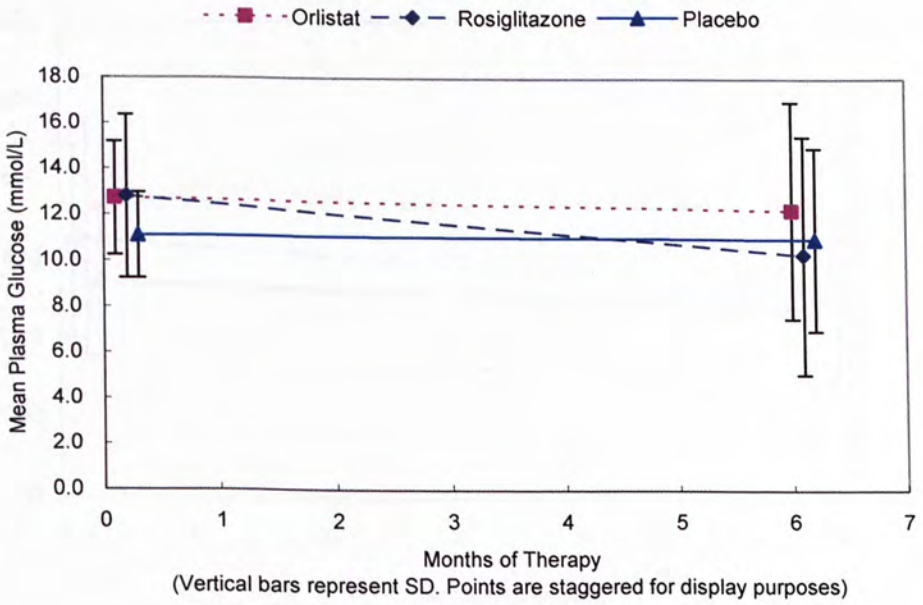

**Figure 3.6: Mean Plasma Glucose Levels after OGTT for Placebo**



### 3.3.1.4.1.1. 2-hr Glucose

When comparing the effects of drug treatments, there is no statistically significant difference. Surprisingly, when the percentage differences in mean 2-hr glucose pre- and post- treatments were compared, the different groups gave no statistically significant result ($p = 0.057$) as well. Within groups, both the control and the orlistat groups had almost no change. However, the rosiglitazone group had a drop ($p = 0.10$), indicating some improvement in the 2-hr glucose value.

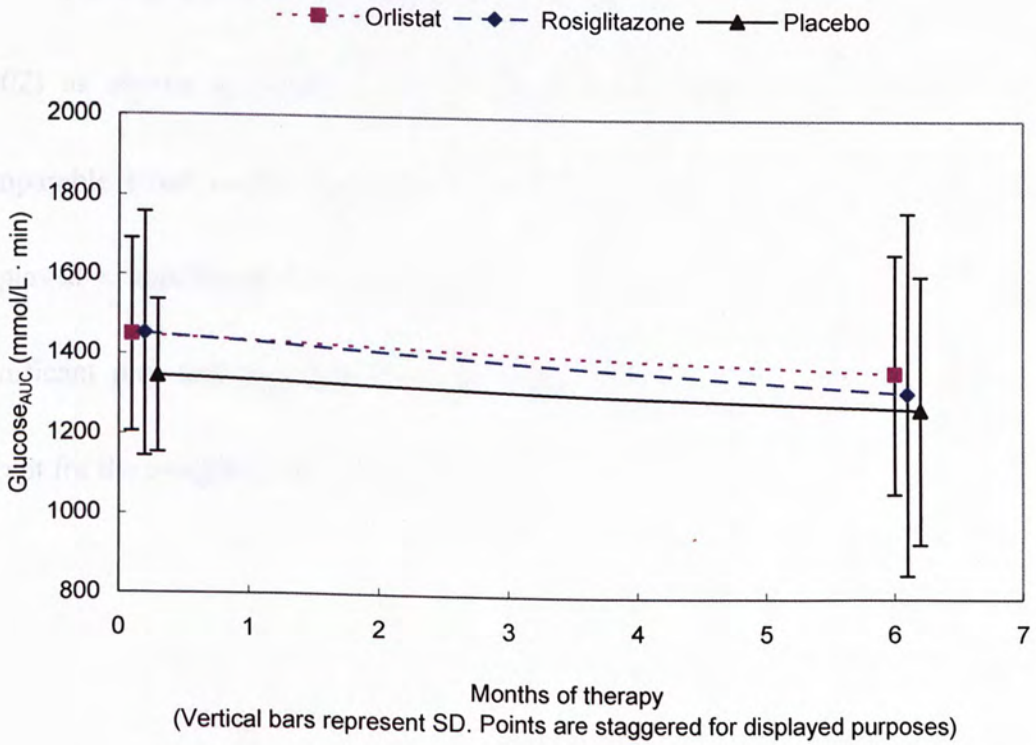
**Figure 3.7: 75g OGTT - 2-hr Glucose**



### 3.3.1.4.1.2. Glucose $_{AUC}$

Similarly, although all three groups showed a decrease in the mean glucose$_{AUC}$ values, there is no statistically significant result within and amongst groups. Comparing the percentage differences in mean glucose$_{AUC}$ before and after treatments of the three groups gave no statistically significant result ( $\chi^2 = 0.570$ , p 0.752).

**Figure 3.8: 75g OGTT - Glucose$_{AUC}$**



#### 3.3.1.4.2. Insulin

The time plot (Figures 3.9, 3.10 and 3.11) for insulin levels after 75g OGTT showed no statistical difference in the three groups at baseline. However, after six months of therapy, for the rosiglitazone group, there is an obvious reduction in the plasma insulin levels when compared with the control ($p < 0.0005$). In contrast, orlistat showed no obvious difference in the plasma insulin levels ($p = 0.831$).

##### 3.3.1.4.2.1. 2-hr Insulin

There is a statistically significant difference between treatment groups ($p = 0.002$) as shown in Figure 3.12, with the orlistat group displaying an almost comparable trend to the control ($p = 0.98$). In contrast, the rosiglitazone group displayed a significant treatment effect ($p = 0.004$). Within groups, there is no significant pre- and post-treatment difference for the control and orlistat groups, except for the rosiglitazone group ($p = 0.006$).

**Figure 3.9: Mean Insulin after OGTT for Orlistat**

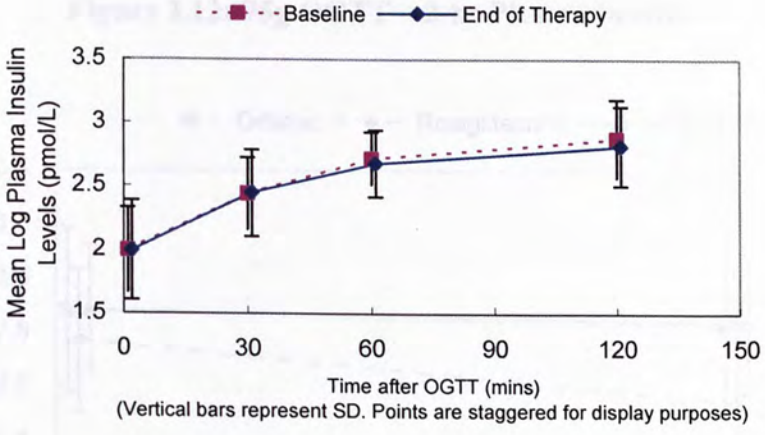



**Figure 3.10: Mean Insulin after OGTT for Rosiglitazone**

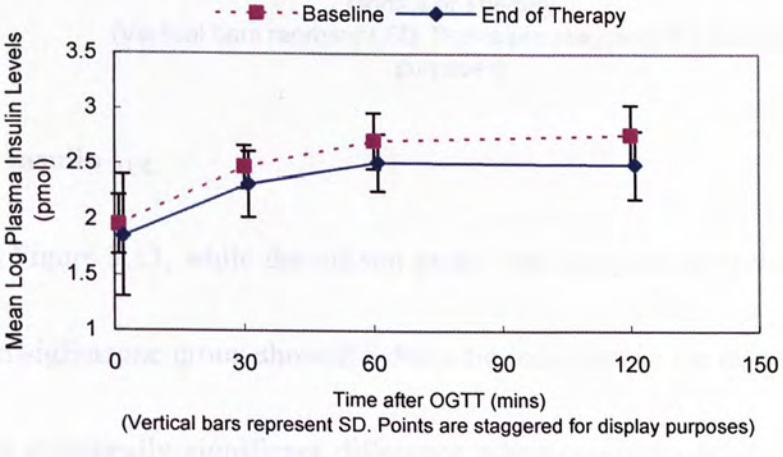



**Figure 3.11: Mean Insulin after OGTT for Placebo**

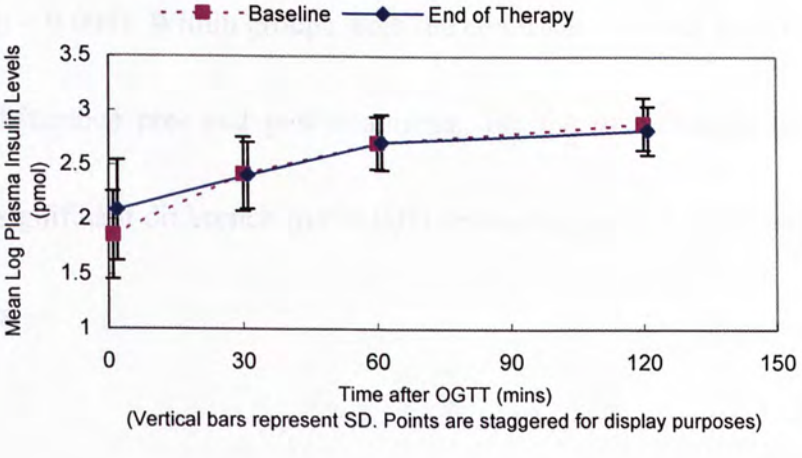
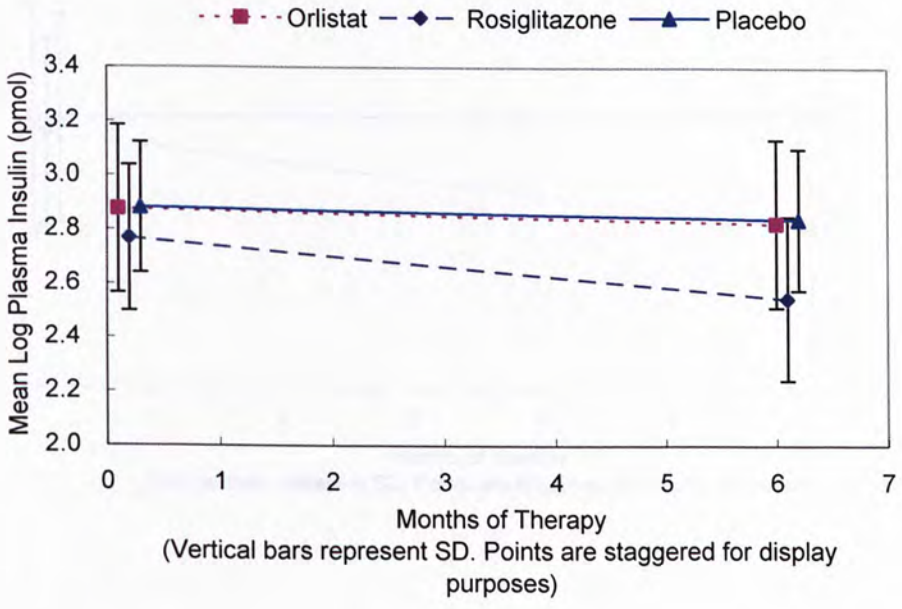


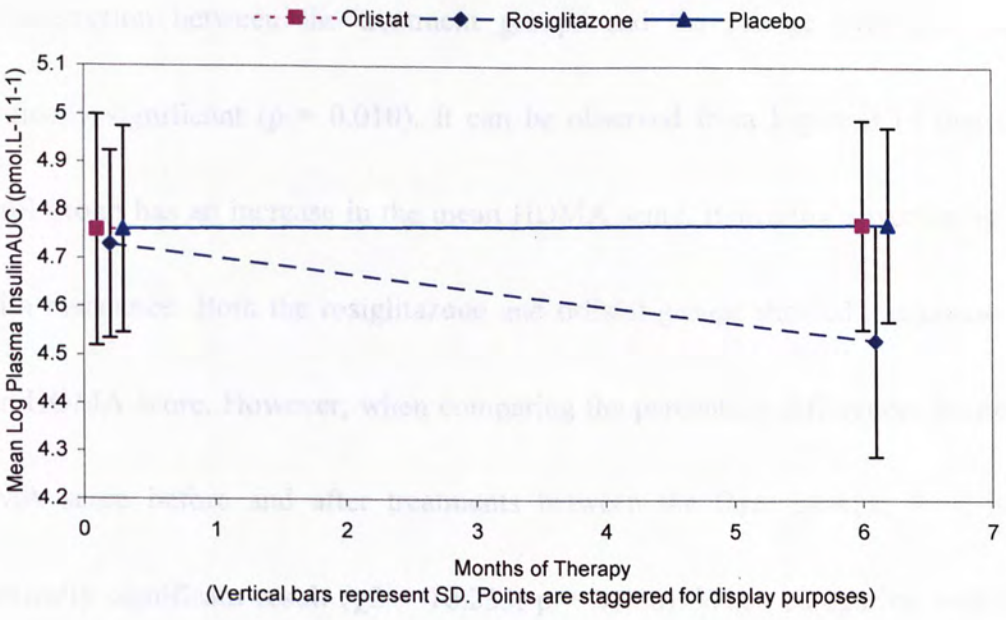
**Figure 3.12: 75g OGTT – 2-hr Plasma Insulin**




### 3.3.1.4.2.2. Insulin $_{AUC}$

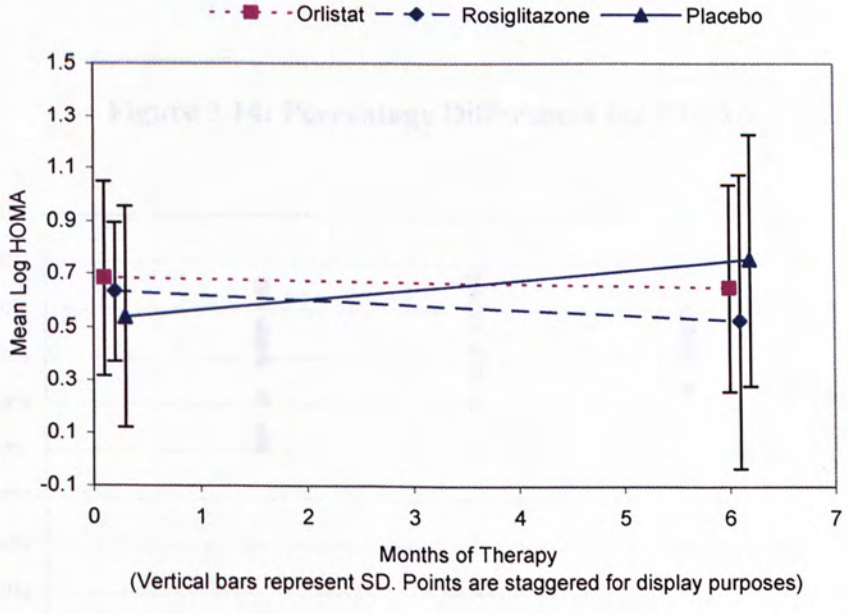
From Figure 3.13, while the orlistat group was comparable to the control (p = 1.00), the rosiglitazone group showed a dramatic reduction in the mean insulin$_{AUC}$ value, with a statistically significant difference when compared with control (p = 0.016). The percentage differences pre- and post treatments were also statistically significant (p = 0.005). Within groups, both the control and orlistat group showed no significant difference pre- and post-treatments, but the rosiglitazone group had a statistically significant difference (p = 0.001), indicating a great improvement in the insulin levels.

**Figure 3.13 : 75g OGTT – $Insulin_{AUC}$**




(Vertical bars represent SD. Points are staggered for display purposes)

**Figure 3.14: HOMA Scores**




(Vertical bars represent SD. Points are staggered for display purposes)

### 3.3.1.5. HOMA Scores

The interaction between the treatment groups and the change over time was statistically significant ($p = 0.010$). It can be observed from Figure 3.14 that the control group has an increase in the mean HOMA score, indicating a worsening of insulin resistance. Both the rosiglitazone and orlistat groups showed a decrease in mean HOMA score. However, when comparing the percentage differences in mean HOMA score before and after treatments between the three groups, there is a statistically significant result ($\chi 2 = 10.235$, $p = 0.006$). When comparing with the control, both groups displayed significant differences (rosiglitazone group $p = 0.005$, orlistat group $p = 0.026$).

**Figure 3.14: Percentage Differences for HOMA**

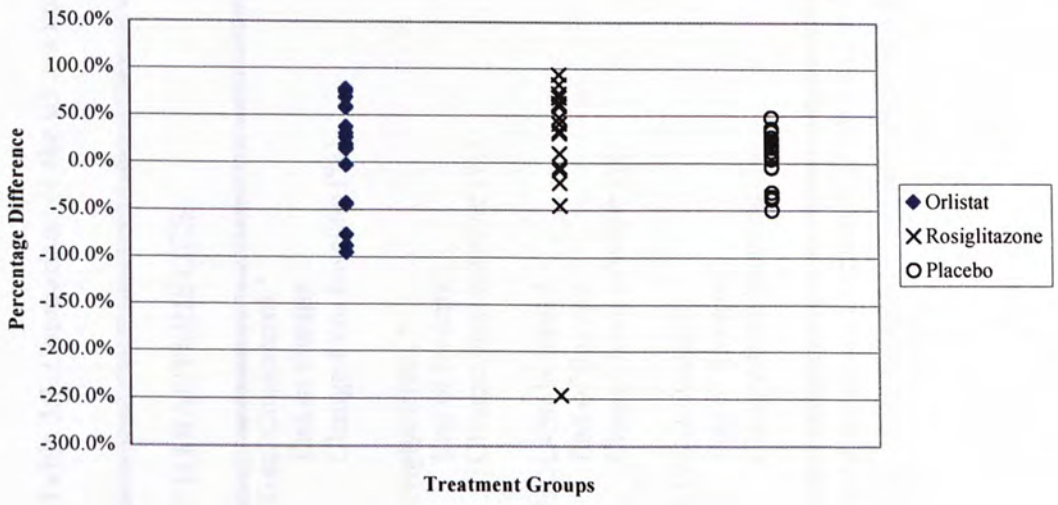


**Table 3.7. Comparison of the serum lipid profiles of study subjects at the end of study.**

| CHARACTERISTICS | Orlistat ( n = 19 ) | Rosiglitazone ( n = 20 ) | Placebo ( n = 19 ) | P-value |
|---|---|---|---|---|
| Total Cholesterol * | | | | |
| End of therapy | 4.58 ± 0.96 | 5.40 ± 0.84 | 5.08 ± 1.05 | |
| Change from baseline (%) | -12.05 ± 0.10 ‡ | 5.52 ± 0.14 | 2.30 ± 0.19 | 0.001 |
| Triglycerides * | | | | |
| End of therapy | 1.80 (1.19 – 3.75) | 1.58 (1.29 – 2.31) | 1.69 (1.14 – 2.62) | |
| Change from baseline (%) | -4.07 ± 0.34 | -4.39 ± 0.67 | 64.55 ± 1.49 | 0.037 |
| HDL-cholesterol * | | | | |
| End of therapy | 1.28 ± 0.32 | 1.41 ± 0.41 | 1.42 ± 0.50 | |
| Change from baseline (%) | -0.46 ± 0.08 | -2.92 ± 0.13 | 3.60 ± 0.15 | 0.789 |
| LDL-cholesterol | | | | |
| End of therapy | 2.22 ± 0.71 | 3.07 ± 0.85 | 2.62 ± 0.63 | |
| Change from baseline (%) | -20.94 ± 0.26 ‡ | 11.63 ± 0.27 | 10.36 ± 0.18 ‡ | 0.001 |

Data are shown as mean ± SD or median (interquartile range), * Data analysed using Kruskal-Wallis Test.

‡ $p < 0.05$ for within groups comparison pre and post treatments.

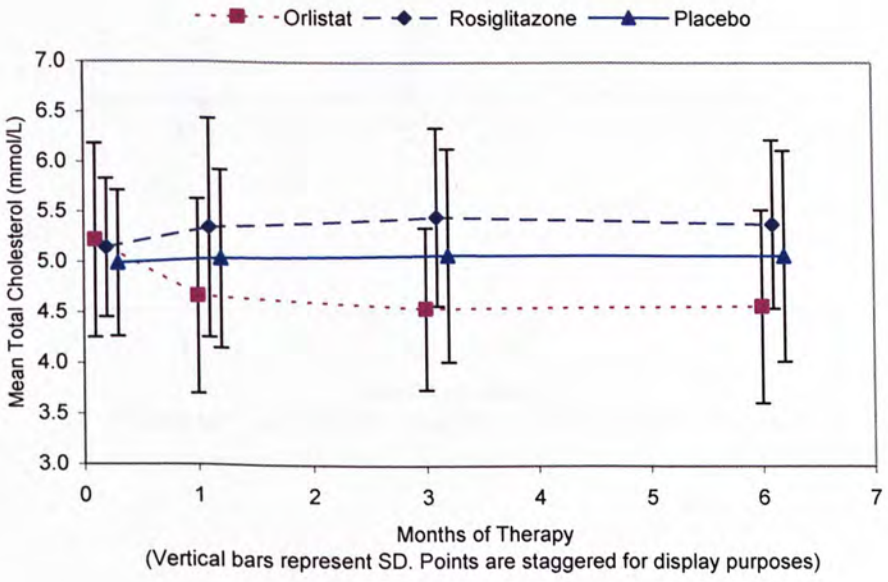
### 3.3.2. Clinical Determinants

#### 3.3.2.1. Lipid Profiles

##### 3.3.2.1.1. Total Cholesterol

There is statistically significant difference when comparing the effects of drug treatments on total cholesterol ($p = 0.001$). However, when compared to the control group, both the rosiglitazone and orlistat groups had no significant difference ($p = 0.090$ and $0.091$ respectively). In contrast, when comparing within the groups itself, the orlistat group had a significant improvement (p-value $< 0.0005$) from baseline, while there is no statistical difference for the control and rosiglitazone groups.

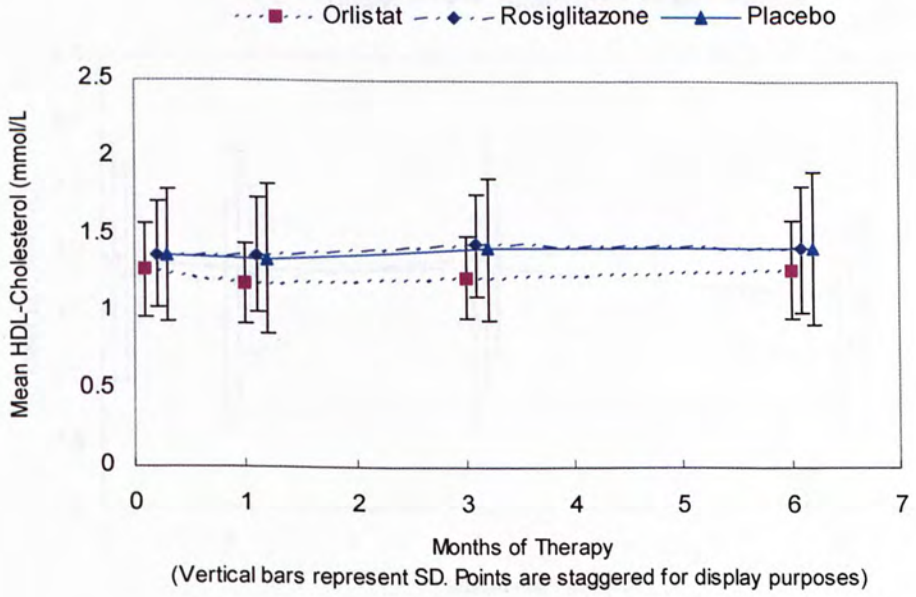
**Figure 3.16: Total Cholesterol**



### 3.3.2.1.2. HDL-Cholesterol

Although there is a statistically significant treatment effect, indicating a difference between therapies on HDL-cholesterol levels ($p = 0.038$), but when compared to the control, both the rosiglitazone and orlistat groups displayed no statistically significant difference ($p = 0.88$ and 0.09 respectively). In addition, comparing within groups showed no statistically difference pre- and post-treatments in all three groups.

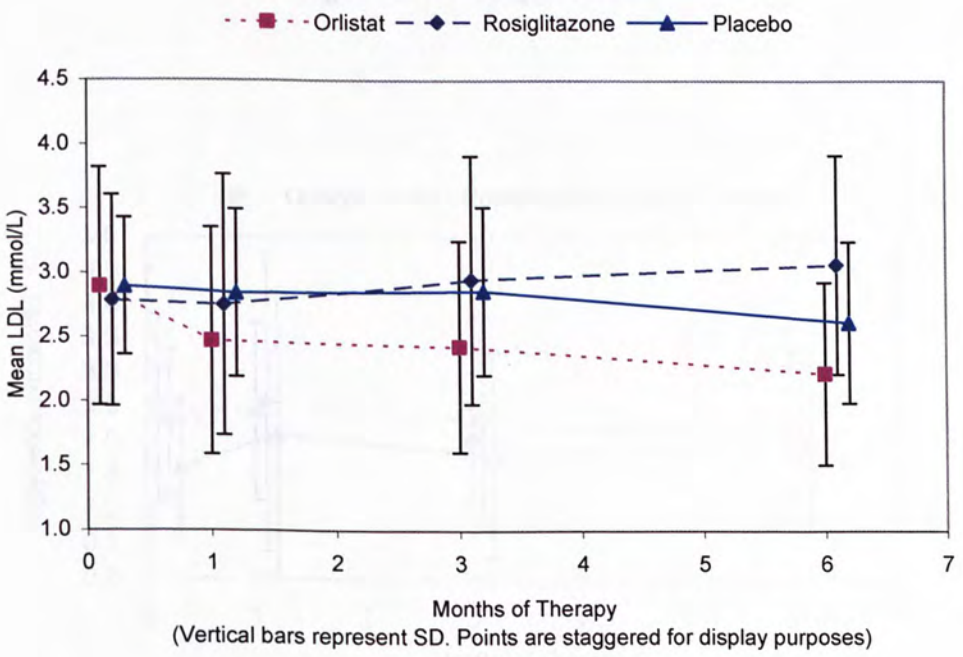
**Figure 3.17: HDL-cholesterol**



### 3.3.2.1.3. LDL-Cholesterol

There is a statistically significant treatment effect (p = 0.011) on LDL-cholesterol. The post hoc tests indicated that the orlistat group is marginally statistically different (p = 0.043) while the rosiglitazone group is no difference (p = 0.784) when compared to the control group. In contrast, when comparing within the groups itself, the orlistat group had a significant improvement (p = 0.002) from baseline, while there is no statistical difference for the control and rosiglitazone groups.

**Figure 3.18: LDL-Cholesterol**



### 3.3.2.1.4. Triglycerides

From Figure 3.19, although the baseline triglycerides for the three groups were not comparable at entry, their endpoints were almost comparable despite the fact that the placebo group had a much lower triglyceride level to start with. The control groups showed an increase from baseline while the other two groups had a reduction. The effects of drug treatments on triglycerides were statistically different amongst the three groups ($p = 0.02$). When compared to the control, both the rosiglitazone and orlistat groups displayed statistically significant difference ($p = 0.037$ and 0.022 respectively).

**Figure 3.19: Triglycerides**

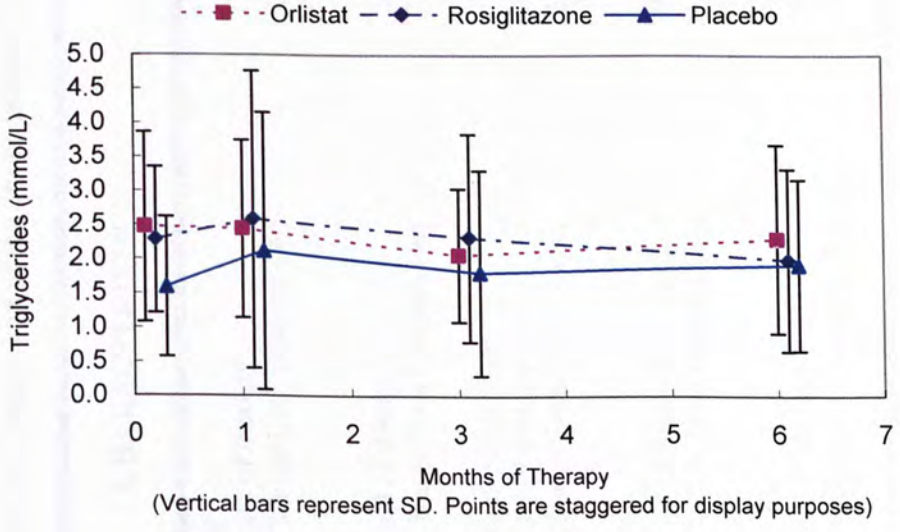


**Table 3.8 Comparison of the anthropometric parameters of the subjects at the end of the study.**

| CHARACTERISTICS | Orlistat ( n = 19 ) | Rosiglitazone ( n = 20 ) | Placebo ( n = 19 ) | P-value |
|---|---|---|---|---|
| Weight | | | | |
| End of therapy | 71.22 ± 15.47 | 70.60 ± 13.09 | 74.73 ± 15.36 | |
| Change from baseline (%) | 2.95 ± 0.03 ‡ | -0.96 ± 0.04 | 0.73 ± 0.03 | 0.002 |
| BMI | | | | |
| End of therapy | 27.05 ± 4.76 | 28.62 ± 4.37 | 28.97 ± 4.98 | |
| Change from baseline (%) | 2.95 ± 0.03 ‡ | -0.96 ± 0.04 | 0.73 ± 0.03 | 0.002 |
| Waist circumference * | | | | |
| End of therapy | 89.65 ± 10.65 | 89.98 ± 10.30 | 91.34 ± 9.53 | |
| Change from baseline (%) | 2.30 ± 0.03 ‡ | 0.49 ± 0.04 | 0.64 ± 0.03 | 0.049 |
| Hip * | | | | |
| End of therapy | 97.74 ± 7.92 | 101.28 ± 8.05 | 98.24 ± 23.84 | |
| Change from baseline (%) | 1.25 ± 0.02 ‡ | -1.54 ± 0.02 ‡ | 4.60 ± 0.21 | 0.002 |
| Body Fat * | | | | |
| End of therapy | 36.28 ± 5.05 | 54.84 ± 72.73 | 39.41 ± 5.90 | |
| Change from baseline (%) | 0.94 ± 0.04 | -3.72 ± 0.06 ‡ | -3.10 ± 0.05 ‡ | 0.006 |

Data are shown as mean ± SD, * Data analysed using Kruskal-Wallis Test.

‡ $p < 0.05$ for within groups comparison pre and post treatments.

### 3.3.2.2. Anthropometric Evaluations

#### 3.3.2.2.1. Body Weight

It is shown in Figure 3.20 that there is a mean weight loss in the orlistat group but for the rosiglitazone group, there is a mean weight gain instead. There is a statistically significant difference between the groups ($p = 0.001$) on the weight differences. When comparing with the control, the orlistat group had a mean weight loss of $-0.739 \pm 0.33$ kg ($p = 0.050$) while the rosiglitazone group has a mean weight gain of $1.064 \pm 0.33$ ($p = 0.003$).

**Table 3.9 : Weight Gain at 1, 3 and 6 month**

*Results are expressed as changes in kg of the body weight when compared with baseline*

| Weight Changes (Kg) | Orlistat Mean + SD (Range) | Rosiglitazone Mean + SD (Range) | Control Mean + SD (Range) | P-value |
|---|---|---|---|---|
| 1 Month | -0.54 ± 0.9 (-1.9 – 1.2) | 0.13 ± 1.2 (-3.0 – 2.0) | -0.52 ± 1.4 (-3.8 – 1.2) | 0.143 |
| 3 month | -1.02 ± 1.5 (-4.0 – 1.6) | -2.5 ± 1.5 (-2.5 – 4.0) | -0.54 ± 2.0 (-5.8 – 3.0) | **0.003** |
| 6 month | -2.12 ± 1.9 (-6.5 – 1.4) | 0.73 ± 2.5 (-5.0 – 5.4) | -0.41 ± 2.2 (-6.3 – 3.2) | **0.001** |

**Figure 3.20: Mean Weight Differences**

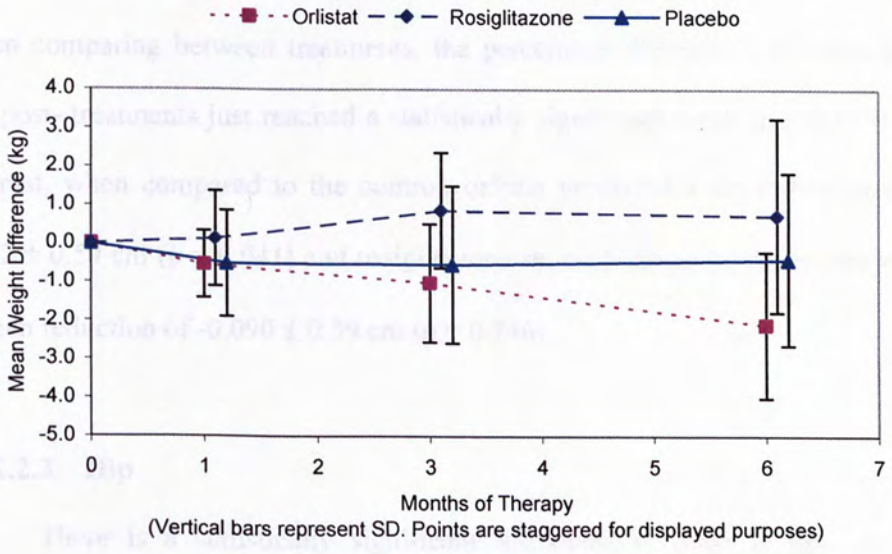
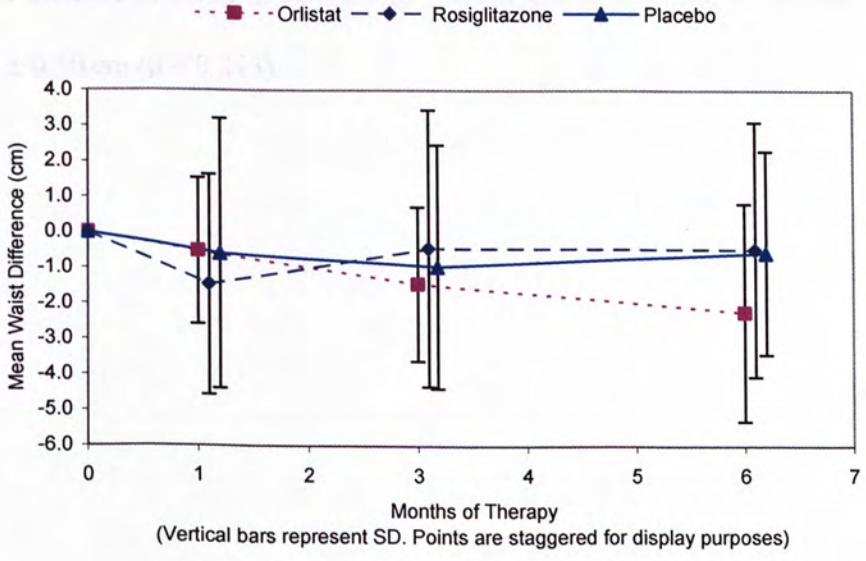



**Figure 3.21: Mean Waist Differences**



#### 3.3.2.2.2. Waist Circumference Difference

Figure 3.21 showed that orlistat displayed a steady decrease in waist circumference while rosiglitazone had an increase since the start of therapy. When comparing between treatments, the percentage differences in waist pre- and post- treatments just reached a statistically significant result ($p = 0.049$). In contrast, when compared to the control, orlistat produced a net reduction of $-0.702 \pm 0.59$ cm ($p = 0.041$) and rosiglitazone showed almost no difference with a mean reduction of $-0.090 \pm 0.59$ cm ($p = 0.746$).

#### 3.3.2.2.3. Hip

There is a statistically significant difference between groups on the percentage differences in hip pre- and post-treatment ($p = 0.002$). From Figure 3.22, there is almost no change in the control group on the hip difference throughout the study. In contrast, when compared to the control, rosiglitazone had an increase of $0.755 \pm 0.50$ cm ($p = 0.16$) and orlistat had a decrease of $-0.658 \pm 0.50$ cm ($p = 0.243$).

**Figure 3.22: Mean Hip Differences**

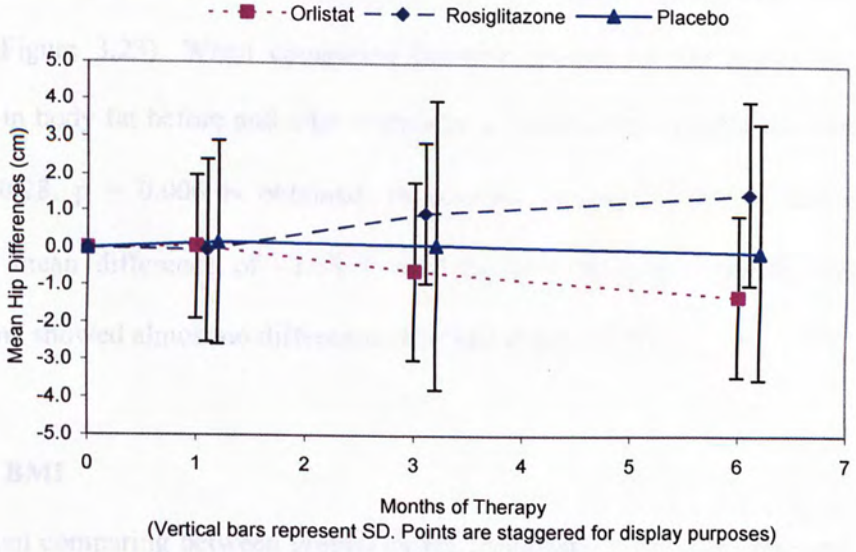
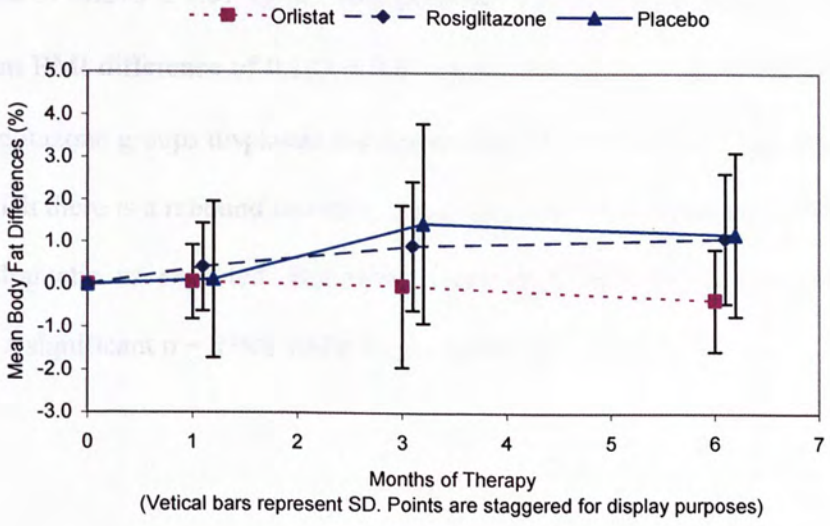



**Figure 3.23: Body Fat Differences**



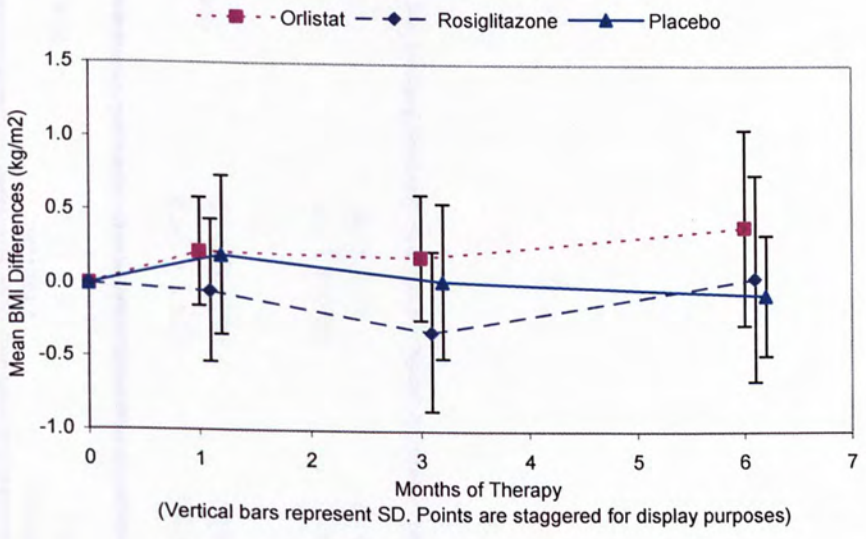
### 3.3.2.2.4. Body Fat

Both the control and rosiglitazone group have a net increase in the mean body fat differences at the end of treatment while the orlistat group had a net decrease (Figure 3.23). When comparing between groups on the percentage difference in body fat before and after treatment, a statistically significant result of $\chi^2 = 10.28$, $p = 0.006$ is obtained. In contrast to control, orlistat has a significant mean difference of $-1.03 \pm 0.42$ % ($U = 89.0$, $p = 0.008$) and rosiglitazone showed almost no difference ($U = 180.0$, $p = 0.779$).

### 3.3.2.2.5. BMI

When comparing between groups on the percentage differences pre- and post-treatments, there is a statistically significant difference of $\chi^2 = 14.60$, $p = 0.001$. Figure 3.24 shows that the control group has almost no change in the BMI values at the end of the treatment while orlistat had a reduction with a mean BMI difference of $-0.270 \pm 0.07$ kg/m$^2$. Rosiglitazone has a slight increase, resulting in a mean BMI difference of $0.103 \pm 0.07$ kg/m$^2$. Interestingly, both the orlistat and rosiglitazone groups displayed maximum reduction in the first three months, after which there is a rebound increase, explaining why the differences in BMI is not as dramatic as expected. But when comparing with the control, orlistat produce a significant $p = 0.008$ while for rosiglitazone $p = 0.087$.

**Figure 3.24: BMI Differences**




### 3.3.2.3. Blood Pressure

As shown in table 3.10, there are no statistically significant differences for both the mean systolic and diastolic blood pressure before and after treatment in all the three groups.

### 3.3.2.4. RCCA and LCCA

Tables 3.11 showed that there are no statistically significant differences in the wall thickness of both the right and left carotid arteries before and after treatment in all the three groups.

**Table 3.10 Comparison of blood pressure of study subjects at the end of study.**

| CHARACTERISTICS | Orlistat ( n = 19 ) | Rosiglitazone ( n = 20 ) | Placebo ( n = 19 ) | P-value |
|---|---|---|---|---|
| Systolic BP | | | | |
| End of therapy | 131.6 ± 13.2 | 134.7 ± 12.9 | 139.0 ± 15.4 | |
| Change from baseline (%) | 0.26 ± 0.13 | -1.11 ± 0.10 | -0.13 ± 0.11 | 0.925 |
| Diastolic BP | | | | |
| End of therapy | 77.9 ± 9.9 | 77.9 ± 9.2 | 80.4 ± 11.9 | |
| Change from baseline (%) | 0.37 ± 0.13 | -3.65 ± 0.10 | 2.37 ± 0.09 | 0.208 |

Data are shown as mean ± SD

**Table 3.11 Comparison of the wall thickness of the right and left common carotid arteries of study subjects at the end of study.**

| CHARACTERISTICS | Orlistat (n = 19) | Rosiglitazone (n = 20) | Placebo (n = 19) | P-value |
|---|---|---|---|---|
| RCCA | | | | |
| • Proximal | | | | |
| End of therapy | 0.69 ± 0.16 | 0.72 ± 0.27 | 0.64 ± 0.15 | |
| change from baseline (%) | -3.86 ± 0.36 | -5.90 ± 0.33 | 5.51 ± 0.27 | 0.199 |
| • Mid | | | | |
| End of therapy | 0.67 ± 0.15 | 0.66 ± 0.15 | 0.63 ± 0.16 | |
| change from baseline (%) | -1.59 ± 0.35 | -4.86 ± 0.34 | -1.85 ± 0.28 | 0.937 |
| • Distal | | | | |
| End of therapy | 0.88 ± 0.24 | 0.86 ± 0.34 | 0.87 ± 0.27 | |
| change from baseline (%) | 1.88 ± 0.41 | -13.47 ± 0.37 | -17.40 ± 0.55 | 0.468 |
| LCCA | | | | |
| • Proximal | | | | |
| End of therapy | 0.76 ± 0.19 | 0.72 ± 0.21 | 0.70 ± 0.17 | |
| change from baseline (%) | 0.42 ± 0.34 | 1.91 ± 0.19 | -10.59 ± 0.33 | 0.561 |
| • Mid | | | | |
| End of therapy | 0.77 ± 0.25 | 0.80 ± 0.37 | 0.78 ± 0.25 | |
| change from baseline (%) | 6.55 ± 0.30 | -2.91 ± 0.24 | -20.94 ± 0.46 | 0.312 |
| • Distal | | | | |
| End of therapy | 0.85 ± 0.22 | 0.8 ± 0.32 | 0.84 ±0.22 | |
| change from baseline (%) | 2.91 ± 0.36 | 2.72 ± 0.26 | -10.04 ± 0.59 | 0.935 |

Data are shown as mean ± SD. All data analysed using Kruskal-Wallis Test.

### 3.3.2.5. Other outstanding measurements

There are a number of other outstanding results from this study that is outside the scope of this thesis. These included the assessment of visceral obesity by magnetic resonance imaging (MRI) and metabolic cart. Results were not available at the time of writing, but the inclusion of these results would make this study more meaningful and significant.

## 3.4. Side Effects experienced

All the patients on orlistat had the typical gastrointestinal adverse effects such as oily stools and increased defaecation. Other common side effects observed in all three groups included skin rash (about 0.5%) and dizziness. The rosiglitazone and control groups also had other gastrointestinal adverse effects (1%) such as flatulence and other gastrointestinal disturbances (diarrhoea, constipation and nausea). Most side effects resolved as the treatment progressed, with the exception from the orlistat group who resolved soon after treatment ended.

# Chapter Four

# Discussion and Conclusion

## 4.1. Summary of the results

The main aim of the study was to determine whether orlistat and rosiglitazone improved the metabolic environment of Chinese patients affected by the metabolic syndrome. All recruited patients exhibited some or all of the characteristics of the metabolic syndrome, which included glucose intolerance, android obesity, hypertension, dyslipidaemia, hyperinsulinaemia and insulin resistance. The efficacy and side effects of orlistat and rosiglitazone were evaluated in 63 Hong Kong Chinese subjects recruited at the Prince of Wales Hospital. Similarities of baseline characteristics of subjects between groups (Table 3.1 to 3.3) indicated that the comparisons made between the groups following treatment are valid.

### 4.1.1 Effects of Diet and Lifestyle Changes

In general, although patients in the control group had little or no changes in the major glycaemic indices, cholesterol, weight and android obesity, there is still some degree of deterioration in their insulin resistance status, as reflected in the increasing fasting insulin levels, HOMA scores, triglycerides, LDL-cholesterol, hip and body fat levels. This is consistent with the metabolic changes associated with the metabolic syndrome as described in Table 1.1.

There is also a thickening of the carotid arteries, possibly due to insulin resistance. Although statistically insignificant, there is a 21% increase in thickness at the mid left carotid artery and a 17% increase at the distal right carotid artery.

### 4.1.2 Effects of Orlistat

In contrast, patients on orlistat demonstrated improved serum lipid, especially on the reduction of total cholesterol (12.1%) and LDL-cholesterol (20.9%), as anticipated from orlistat's inhibitory effect on the absorption of dietary fat. Although orlistat does not produce any statistically significant improvements in the HDL-cholesterol (0.5% drop) nor triglycerides (4% reduction) levels, this finding is consistent with clinical studies (Hollander PA et al., 1998 and Torgerson JS et al., 2004). Interestingly, the orlistat group was almost comparable with the control group on the percentage difference of pre- and post-treatments for the fasting insulin (Table 3.4). However, after 75g-OGTT, there is a slight improvement in the 2-hr insulin and $insulin_{AUC}$, indicating some improvement in insulin resistance.

The changes for the orlistat group are most apparent after 3 months of therapy ($HbA_{1C}$, total cholesterol, triglycerides and BMI). Improvements in the anthropometric parameters (weight changes, waist and hip differences and body fat differences) are most apparent after 6 months of treatment.

Weight loss has been reported to improve glucose tolerance, increase insulin sensitivity and improve lipid profiles. However, in this study, improvements in the anthropometric evaluations did not produce any significant changes in the glycaemic indices for the orlistat group, except for a mild reduction in the glycaemic indices and HOMA scores. This may be due to the fact that most clinical trials were conducted over a period of at least one year, with a large sample size. Hence, the effects of orlistat on the glycaemic indices of blood glucose and insulin levels may not be apparent in this study, which was limited by the comparatively small sample size and a short duration of therapy.

### 4.1.3 Effects of Rosiglitazone

The rosiglitazone group, in comparison, exhibits maximum improvements in the glycaemic indices and HOMA scores, which is consistent with rosiglitazone's role as an insulin-sensitiser. Although not statistically significant as compared with placebo or orlistat, the rosiglitazone group had a mild increase in the total cholesterol, triglycerides, and HDL-cholesterol levels. There is a 12% increase in LDL-cholesterol, which occurs primarily after 3 months of therapy and remains elevated above baseline to the end of therapy. These findings are consistent with other clinical

trials involving thiazolinediones, as discussed earlier in Chapter 1 (Thomas JC et al. 2001 and Khan MA et al 2002.).

Based on the pharmacological mechanisms of action, rosiglitazone promotes increased storage of glucose in cells, resulting in increased weight, hence resulting in the modest weight gain, increase in hip circumference and total body fat, as reflected in the rosiglitazone group. Rosiglitazone has been found to increase subcutaneous fat area but not significantly alter intra-abdominal fat area (SmithKline Beecham Pharmaceuticals, Prescribing information 2001), perhaps explaining why there is no significant increase in the mean waist difference.

## 4.2. Implications for Therapy

It has been proposed that the metabolic syndrome is a powerful determinant of type 2 diabetes and cardiovascular disease (Reaven DM 1988, DeFronzo RA et al 1991). The features of the metabolic syndrome are observed not only in type 2 diabetes mellitus and in patients before they develop diabetes, but also in a large proportion of individuals with insulin resistance who are relatively euglycaemic and who may never develop type 2 diabetes mellitus (Haffner SM, 1990).

Most metabolic syndrome patients are at a much greater risk for atherothrombotic events than are patients who have impaired glucose tolerance or

type 2 diabetes mellitus (Lillioja S et al 1993, Martin BC 1992). Cardiovascular risk is not increased by hyperglycaemia alone. Instead, it is the accompanying metabolic abnormalities combining with hyperglycaemia that impart the high risk for cardiovascular atherothrombotic events (Reaven GM 1988).

### 4.2.1 Management of metabolic syndrome

The primary goals of treating metabolic syndrome are prevention of type 2 diabetes mellitus and cardiovascular events. According to the American Diabetes Association and in the NCEP ACEP III report 2001, the management of the metabolic syndrome involves reducing underlying causes and treating associated nonlipid and lipid risk factors. Treatment must address the multipathologic process of metabolic syndrome, with each component identified and aggressively targeted for treatment (Table 4.1). Notwithstanding the difficulty and expense of long-term prospective intervention, treating individuals with the metabolic syndrome at early stages promises to yield real savings in the later financial costs associated with advanced cardiovascular disease (Russell JC 2001).

**Table 4.1: Approaches to the treatment of the metabolic syndrome**

- Multi-factorial behavioural changes
- Therapeutic lifestyle interventions
  - Increased physical activity
  - Weight reduction
  - Prudent diet
    - Increase intake of fruits and vegetables
    - Decreased intake of saturated fats
    - Increased intake of foods with decreased glycaemic index
- Pharmacological therapy
  - Aspirin
  - Antihypertensive therapy (RAAS Blockers)
  - Lipid lowering therapy
  - Insulin Sensitisers.

### 4.2.2 Early Diagnosis

Given the slow, asymptomatic development of cardiovascular disease in the metabolic syndrome, a rational approach to the growing incidence of overt type 2 diabetes and the associated cardiovascular disease is early diagnosis and preventative treatment. This implies effective screening for the early stages of disease progression even in the absence of any clinically significant disease. The target population of interest consists of both genders having abdominal obesity, a factor that can most efficiently and accurately be identified by measuring waist circumference. Individuals with elevated plasma insulin, impaired glucose and an excessive insulin

response can be identified using the relatively simple oral glucose tolerance test. Other routine laboratory tests should reveal dyslipidaemia, hyperuricaemia and microalbuminuria. As demonstrated in this study, most of these metabolic syndrome traits can be easily detected at any clinical setting. These identified individuals should then be at high priority for dietary, exercise, and pharmacological intervention. However, from our study (as seen in the control group) and other clinical trials (Swinburn BA et al 2001, Wing RR et al 2001), this patient group will not show significant and lasting metabolic improvement without effective pharmacological treatment. This is because while weight loss is achievable in the short-term (6-12 months) once the intensive intervention ends, people drift back to their original weight.

### 4.2.3 Lifestyle modification

Weight reduction and regular physical activity are key elements for prevention and care of metabolic syndrome. Although no particular diet plan or dietary composition has been studied specifically in relation to the metabolic syndrome, the current dietary recommendations, as we had recommended to our study population, include a balanced low-energy diet containing, fruits, vegetables, whole grains, fish,

and lean meats while minimizing fats, salt, simple sugars and highly processed foods (Miranda PJ et al 2005).

Data from the Finnish Diabetes Prevention Study group (522 subjects) concluded that the risk of type 2 diabetes mellitus could be reduced by 58% compared with the control group by instituting therapeutic lifestyle changes in patients with the metabolic syndrome. The therapeutic lifestyle changes in the intervention group (265 subjects) consisted of specific dietary instructions and moderate exercise of ≥ 30 min/day (3.5 hours/week) but subjects in the control group were not offered any specific individualized programs. At the mean duration of 3.2 years, the incidence of impaired glucose tolerance progressing to type 2 diabetes mellitus is 3% per year in the intervention group and 6% per year in the control group.

The Diabetes Prevention Program, Da Qing study, Stop-NIDDM trial and TRIPOD trial have also confirmed that diabetes is preventable, and insulin resistance is decreased by weight loss or exercise, or both (Table 4.2).

In this study, in the control group, four patients who were diagnosed as IGT at the start of therapy became normoglycaemic at the end of the study, with one progressed from diabetes to IGT. This shows that even simple lifestyle intervention is important in slowing the progression of diabetes in high-risk patients.

**Table 4.2. Diabetes Prevention Trials**

| Study | Intervention | Risk Reduction (%) |
|---|---|---|
| Finnish Diabetes Prevention Study | Lifestyle Changes | 58 |
| Da Qing Study | Lifestyle Changes | 31 – 40 |
| Diabetes Prevention Program | Lifestyle Changes, | 53 |
| | Metformin | 31 |
| TRIPOD | Troglitazone | 55 |
| STOP-NIDDM Trial | Acarbose | 25 - 36 |
| WOSCOPS | Pravastatin | 30 |
| HOPE | Ramipril | 34 |

TRIPOD = Troglitazone in the Prevention of Diabetes; STOP-NIDDM = Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; WOSCOPS = West of Scotland Coronary Prevention Study; HOPE = Heart Outcomes Prevention Evaluation

**Table 4.3. Coronary Artery Disease (CAD) Prevention Trials with Statins in Subjects with Diabetes**

| Study | Statin | Subjects (N) | CAD Risk Reduction (%) | |
|---|---|---|---|---|
| | | | Overall | Diabetes |
| HPS | Simvastatin | 20 536 | 25 - 30 | 22 - 33 |
| CARE | Pravastatin | 589 | 23 | 25 |
| 4S | Simvastatin | 202 | 32 | 55 |

HPS = Heart Protection Study; CARE = Cholesterol and Recurrent Events trial; 4S = Scandinavian Simvastatin Survival Study.

### 4.2.4 Pharmacological Targets

#### 4.2.4.1 Statins

As discussed in Chapter 1, the metabolic syndrome is commonly associated with hyperinsulinaemia and a specific abnormal lipid profile, i.e. elevated plasma triglycerides (Carlson LA 1979), low HDL-cholesterol (Castelli WP 1986), and increased VLDL-cholesterol (Stamler J 1986), all of which can predispose to the development of atherosclerosis. Despite the gaps in our understanding, it is clear that effective reduction of the insulin levels and the accompanying VLDL hyperlipidaemia is the first step towards a final therapeutic goal.

In the NCEP report published in July 2004, the coordinating committee of the National Cholesterol Education Program reviewed recent clinical trials for the NCEP ATP II guidelines and recommended the initiation of statins in diabetic patients, especially those with cardiovascular disease (Grundy et al 2004). The benefits of statin therapy in people with diabetes have been observed from the post hoc subgroup analysis of 3 major statin trials (Table 4.3). Patients with diabetes who received pravastatin or simvastatin had fewer coronary artery disease events. Although statins do not alter insulin resistance, the WOSCOPS study (Shepherd J et al 1995) showed that patients treated with pravastatin had a lower incidence of new-onset type 2 diabetes mellitus compared to those on placebo (Table 4.2). In addition,

the HPS support an aggressive immediate approach for the metabolic syndrome, with statin therapy to stabilize at-risk atherosclerotic plaques. The multifactorial regimen of diet, exercise, and statin therapy, therefore, is highly recommended.

#### 4.2.4.2 Fibrates

Drugs in the fibric acid group, including clofibrate, gemfibrozil and fenofibrate, reverse the dyslipidaemia associated with the metabolic syndrome. In the Diabetic Atherosclerosis Intervention Study (DAIS) (Steiner G 2001), a multinational angiographic study of individuals with type 2 diabetes mellitus, fenofibrate-treated subject HAD a 10% reduction in the levels of total cholesterol, 7% decrease in LDL, 6% increase in HDL and a 30% reduction in plasma triglyceride levels.

#### 4.2.4.3 ACE Inhibitors

In the HOPE study (Yusuf S et al 2001) , the ACE inhibitor ramipril was studied to examine its effectiveness in reducing macrovascular and microvascular effects in 3654 diabetic patients and 5720 non-diabetic patient. Ramipril reduced the risk of development of diabetes (primary prevention) by 34% (Table 4.2), exact mechanism on how it does it is unknown.

#### 4.2.4.4 Thiazolidinediones

The early stages of metabolic syndrome consist primarily of insulin resistance with glucose intolerance or overt type 2 diabetes mellitus. These metabolic syndrome patients are likely to be seen by primary care providers. Since clinicians now recognize diabetes mellitus as a cardiovascular disease risk equivalent, in applying the ATP III guidelines, clinicians need to consider both the hyperglycaemia and the cardiovascular sequelae associated with insulin resistance. Hence, insulin sensitisers are indicated as the primary prevention in treating insulin resistance.

In the TRIPOD Study (Buchanan et al 2002), involving 236 Hispanic women with previous gestational diabetes, there is a 55% relative reduction in diabetes progression. Even after a washout period of 8 months, the preventive effects of the drugs were still observed. Therefore, it is possible that troglitazone may affect the natural history of glucose intolerance and may actually prevent diabetes in certain patients, rather than simply delaying its onset.

No clinical trial data to date support the use of pharmacological agents to improve insulin sensitivity in non-diabetic subjects, although this is an area of active interest. In our study, which included non-diabetic patients with glucose intolerance, the results of rosiglitazone were promising. The number of patients who were previously diagnosed as having diabetes dropped in the rosiglitazone group.

Surprisingly, there is a rise in the number of patients having the metabolic syndrome in the rosiglitazone group. However, as consistent with its pharmacological effects as an insulin-sensitiser, six diabetic patients were diagnosed as IGT while another six who were IGT became normoglycaemic. These results indicate that rosiglitazone may have some potential in delaying the onset of type 2 diabetes in high-risk patients.

Although the insulin sensitizing effects of rosiglitazone may not be as apparent due to the small sample size, there is an obvious trend of improvement, indicating a possibility in reducing cardiovascular risk associated with metabolic syndrome. The favourable lipid profile and low incidence of adverse effects provide overall benefits to patients beyond blood glucose control. Although in this study, total cholesterol increases in general, there is a drop in triglycerides and the increase in LDL-cholesterol increased. Even though LDL particle size is not measured in this study, it has been shown that rosiglitazone changes the LDL particles from predominantly small and dense (ie, a more atherogenic profile) to larger, more buoyant and less atherogenic particles (Lebowitz HE 2002). As a result of this shift, the ratio of LDL-cholesterol to apolipoprotein B increases, therefore, plasma LDL-cholesterol concentration increases by 11% in this study. When compared with other anti-diabetic agents, these improved efficacy measures and additional benefits should

have long-term clinical and economic effects when projected over the lifetime of a patient with metabolic syndrome eventually progressing to diabetes.

Published reports suggest that pioglitazone and rosiglitazone have different effects on lipids in patients with type 2 diabetes (King AB 2000, Boyle PJ et al 2002, Khan MA et al 2002, Olansky L et al 2003). However, these studies were either retrospective chart reviews or clinical trials not rigorously controlled for concomitant glucose- and lipid-lowering therapies. Goldberg RB and colleagues recently published a study comparing the lipid and glycaemic effects of pioglitazone and rosglitazone in patients with type 2 diabetes and dyslipidaemia (Goldberg RB et al 2005). It was shown that triglycerides decreased with pioglitazone but increased with rosiglitazone instead. The increase in HDL-cholesterol was also greater with pioglitazone and the increase in LDL-cholesterol was less than rosiglitazone. LDL particle size increased more with pioglitazone too. These findings showed that both thiazolinediones had different effects on plasma lipids independent of glycaemic control or concomitant lipid-lowering or other antihyperglycaemic therapy. When compared with rosiglitazone, pioglitazone may have more favourable effects on lipid profiles, but whether these differences translate into differences for the risk of CVD is not clear.

#### 4.2.4.4.1 Economic Evaluation of Thiazolidinediones

There are no published economic studies on rosiglitazone. However, Coyle D and colleagues conducted an economic evaluation of pioglitazone in the management of type 2 diabetes mellitus in Canada. Using a Markov model to determine the health outcomes and economic impact from the prospective of a provincial ministry of health, it compared treatment strategies with different first-line therapies: pioglitazone, glibenclamide, metformin, diet and exercise. The pioglitazone-based strategy was estimated to reduce the cumulative incidence of severe clinical events and long-term complications by between 23 and 36% and to increase discounted life expectancy by between 0.13 and 0.35 life-years. The discounted incremental cost per life-year gained of a first-line pioglitazone-based strategy was 54 000 Canadian dollars ($Can) compared with metformin, $Can 42 000 compared with glibenclamide and $Can 27 000 compared with diet and exercise.

As thiazolinediones is a more effective treatment for type 2 diabetes mellitus and even metabolic syndrome, it can be projected that this agent may be cost effective for certain patients and may delay the onset of insulin use, which has significant effects on the quality of life. However, ideally, long-term studies are required to support the cost-effectiveness of agents in this class.

### 4.2.4.5 Orlistat

Heymsfield SB et al 2000 conducted a retrospective pooled analysis of three double-blind, randomized, placebo-controlled 2-year trials (Hauptman J et al. 2000, Sjöström L et al 1998, Davidson MH et al, 1999), 675 obese patients IGT patients, 71.6% who were treated with orlistat (n = 359) had normal glucose tolerance at the end of treatment compared with 49.1% (n = 316) in the placebo group (p = 0.04). Also, orlistat recipients had a greater reduction in fasting serum insulin levels and $insulin_{AUC}$. However, in patients classified as diabetes mellitus at baseline, the change in fasting serum insulin levels significantly favoured placebo recipients instead. But in patients with normal glucose tolerance at baseline, compared with placebo, the change from the $insulin_{AUC}$ significantly favoured orlistat (Table 4.4). In addition, fasting serum glucose levels and the $glucose_{AUC}$ had a greater reduction in orlistat when compared to placebo recipients. In the normal glucose tolerance group and IGT group, the reduction from baseline was significantly greater in orlistat than placebo recipients.

These results were consistent in the XENDOS study (Togerson JS et al, 2004) whereby at the end of the 4-year study, the cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% (p = 0.0032). Treatment with orlistat plus lifestyle changes also resulted in early and

significant improvements that were sustained throughout the study (Table 4.5). Total and LDL-cholesterol decreased significantly more with orlistat than placebo, at both 1 and 4 years.

In the XENDOS study, adding orlistat to lifestyle changes produced more weight loss and led to a significantly lower risk of developing type 2 diabetes. It also demonstrated that a weight loss agent in combination with lifestyle changes over 4 years is of greater benefit than lifestyle changes alone for producing long-term weight loss and improvements in cardiovascular risk factors.

In this study, four patients progressed from type 2 diabetes to IGT while one IGT patient became normoglycaemic. There is also a drop in the number of patients with the metabolic syndrome. This is consistent with the findings established by XENDOS and Heymsfield SB et al, suggesting that orlistat may be a useful treatment option in the lowering the risk of developing type 2 diabetes in high-risk patients. It has been shown in this study that the impact of orlistat on lipid parameters was independent of the magnitude of weight loss but was greater in the orlistat group than the control group.

**Table 4.4: Difference in the fasting serum insulin and glucose levels and oral glucose response areas under the curve† (AUCs) at baseline and after treatment * (Adapted from Heymsfield SB et al 2000)**

| | | | | | | P‡ | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Insulin (pmol/L) | | Glucose (mmol/L) | | Insulin | | Glucose | |
| Status | Treatment Group | Fasting | AUC | Fasting | AUC | Fasting | AUC | Fasting | AUC |
| Normal | | | | | | | | | |
| | Placebo | + 4 ± 9 | + 152 ± 88 | - 0.04 ± 0.04 | +0.7 ± 0.4 | | | | |
| | Orlistat | -7 ± 3 | -136 ± 75 | -0.16 ± 0.04 | -1.4 ± 0.4 | 0.40 | 0.03 | 0.02 | < 0.001 |
| IGT | | | | | | | | | |
| | Placebo | +20 ± 12 | +24 ± 189 | 0.10 ± 0.04 | -2.3 ± 1.3 | | | | |
| | Orlistat | -14 ± 7 | -467 ± 188 | -0.42 ± 0.05 | -5.7 ± 1.0 | 0.07 | 0.35 | 0.01 | 0.14 |
| Type 2 Diabetes Mellitus | | | | | | | | | |
| | Placebo | -50 ± 47 | -737 ± 457 | + 0.17 ± 0.16 | -1.5 ± 2.1 | | | | |
| | Orlistat | +34 ± 15 | -480 ± 333 | +0.17 ± 0.42 | -3.8 ± 3.6 | 0.02 | 0.59 | 0.97 | .68 |

* All values are expressed as mean ± SEM
† The AUC units are pmol/L per 3 hours and mmol/L per 3 hours for insulin and glucose respectively.
‡ The difference between placebo and orlistat in the change from baseline to follow-up (least square means).

**Table 4.5: Mean change from baseline of cardiovascular risk factors at years 1 and 4 in all patients (Xendos Study).**

| | Year 1 | | | Year 4 | | |
|---|---|---|---|---|---|---|
| | Placebo + lifestyle | Orlistat + lifestyle | P-value between treatments | Placebo + lifestyle | Orlistat + lifestyle | P-value between treatments |
| **N** | 1,295 | 1,487 | | 567 | 851 | |
| **Diastolic BP (mmHg)** | -2.6 | -3.6 | <0.01 | -1.9 | -2.6 | <0.01 |
| **Systolic BP (mmHg)** | -5.2 | -7.3 | <0.01 | -3.4 | -4.9 | <0.01 |
| **Total Cholesterol (%)** | -1.3 | -8.8 | <0.01 | -2.3 | -7.9 | <0.01 |
| **LDL Cholesterol (%)** | -1.6 | -11.4 | <0.01 | -5.1 | -12.8 | <0.01 |
| **HDL-Cholesterol (%)** | 8.5 | 3.4 | <0.01 | 9.1 | 6.5 | <0.01 |
| **Triglycerides (%)** | -6.3 | -6.2 | <0.05 | 2.9 | 2.4 | Not significant |
| **Waist circumference (cm)** | -7.0 | -9.6 | <0.01 | -4.4 | -6.4 | <0.01 |
| **Venous whole blood glucose (mmol/L)** | | | | | | |
| • **Fasting** | 0.2 | 0.1 | <0.01 | 0.2 | 0.1 | <0.01 |
| • **AUC (nmol·min$^{-1}$ · l$^{-1}$) #** | -27 | -51 | <0.01 | 3 | -14 | <0.01 |
| **Serum insulin (pmol/L)** | | | | | | |
| • **Fasting** | -17.0 | -26.5 | <0.01 | -20.6 | -32.0 | <0.01 |
| • **AUC (pmol·min$^{-1}$ · l$^{-1}$) #** | -11.0 | -14.6 | <0.01 | -8.4 | -10.9 | <0.01 |
| **Fibrinogen (µmol/L)** | 0.3 | .2 | Not significant | -0.5 | -0.4 | <0.05 |
| **Plasminogen activator inhibitor –1 (U/mL)** | -3.0 | -7.1 | <0.01 | 0.1 | -3.0 | <0.01 |

# calculated by trapezoid rule, including all areas above the line $y = 0$, from measurements immediately before and 30, 60, 90, and 120 min after dose.

Although orlistat produced significant reductions in most anthropometric parameters, such effect was not observed in the lipid profile. This is consistent with the findings by Hollander PA et al 1998 and XENDOS. On the other hand, there is no apparent pharmacologic basis for treatment using orlistat compared to lifestyle interventions on parameters of glycaemic control. Indeed, more patients lost a greater amount of weight in the orlistat-treated group, but the relationship between degree of weight loss and improvement in glycaemic control is well-established as discussed earlier.

#### 4.2.4.5.1 Economic Evaluation of Orlistat

Much can be gained economically by reducing bodyweight to help patients gain better control of their fasting plasma glucose (FPG) and glycosylated haemoglobin $A_{1C}$ ($HbA_{1C}$) values. However, most type 2 diabetes medications cause weight gain, and have been shown to aggravate blood glucose control and decrease the clinical effectiveness of treatment (DeFronzo RA 1999).

Orlistat therapy yielded cost savings in a modeling study, available as an abstract (Lee KK et al 2001). It was estimated that in IGT patients, 1.9% of orlistat recipients would progress to type 2 diabetes, as compared with 8% of patients receiving dietary therapy alone. At the end of the 1 year's treatment, the total cost of

managing diabetes mellitus was estimated to be $HK8187 and $HK34 469 in recipients of orlistat plus dietary therapy and dietary therapy alone, respectively. After 2 years' treatment, the total cost of managing diabetes mellitus was $HK23 390 and $HK100 123 in the corresponding treatment groups.

Maetzel A et al 2003 used the Markov state transition model to evaluate the cost effectiveness of orlistat in addition to standard type 2 diabetes treatment (sulphonylureas, metformin, or insulin plus diet and physical activity) in the treatment of overweight and obese patients with type 2 diabetes in a US-based healthcare setting from the perspective of the healthcare provider. It demonstrated that treatment with orlistat increased event-free life expectancy by 0.13 years over 11-year period. Average treatment costs were estimated to be $US19 987 in the orlistat group compared with $US18 865 in the group that received diabetes medication and weight management alone. This translated into a cost-effectiveness ratio of $US8327 per event-free life-year gained. The authors concluded that adding orlistat as a pharmacological treatment to conventional diabetes and weight management approaches seems to be a cost-effective treatment option for overweight and obese patients with type 2 diabetes.

A Belgian analysis found orlistat to be cost-effective, costing $US2996 per life-year gained in patients with type 2 diabetes, hypertension and

hypercholesterolaemia and $US17 298 per life-year gained (2000 values) in patients with diabetes alone (Lamotte M et al 2002).

As healthcare costs have continued to rise, the issues of cost and cost effectiveness for both the health system and society have become increasingly important. The above studies demonstrated that it might be viable and economical to use orlistat to treat the metabolic syndrome in the long run.

## 4.3 Limitations of the study

### 4.3.1 Small sample size

This study was limited by a small sample size of 63 participants of which 58 (92%) completed the study. During the period of study, the outbreak of the Severe Acute Respiratory Syndrome (SARS) occurred and Hong Kong is very badly affected. There is difficulty in patient recruitment as people shunned away from hospitals.

Although a treatment trend may be seen in many parameters such as HbA1c, FPG, triglycerides, HDL-cholesterol and waist circumference differences, there is no statistical significance. In comparison, other clinical trials such as those conducted by Lebovitz HE et al 2001 and the XENDOS study showed significant changes in these parameters. The sample size employed in these studies is very much bigger (n = 169

and n = 1487 respectively), perhaps explaining why such results were not reflected in this study.

### 4.3.2 Short period of study

Both patient recruitment and treatment regimen took around 7 months and the study was ended in approximately three years although this is a six-months study. The reason for the long duration of the study was mainly due to the occurrence of SARS outbreak, which resulted in an approximately eight-month break in patient recruitment until the situation improved. The effects of treatments (lifestyle intervention especially) on reducing clinical cardiovascular events may be more apparent if the duration of study is longer as reflected in the UKPDS, DPP and XENDOS.

### 4.3.3 Adherence to lifestyle modifications

A dietitian recommended a low caloric diet and ≥ 30-minute daily aerobic exercise regimen was advised after patient recruitment. These recommendations were emphasised at every patient visit. However, we do not have any suitable tools to monitor the patient adherence to these recommendations, and there is a lack of documentation of dietary habits and physical activity. That is why there was no

significant weight loss over a period of six months for the lifestyle intervention, in contrast to other clinical trials such as UKPDS and DPP.

### 4.3.4 Analytical assays

Due to the limited amount of finance available, the analytical assays of each patient's plasma glucose and insulin levels after 75g-OGTT was performed once with no repeats conducted, exposing the results to chance. Therefore, the conclusions related were based on a single test result and may not be as convincing.

### 4.3.5 Follow up after end of study

A follow up after the end of the study may be able to address issues such as the sustainability of treatments and long-term adverse events, but limitations set by increasing costs of study medications and laboratory analysis restricted the scope of the study. Also, part of the patients recruited earlier refused to be followed-up during the SARS outbreak.

### 4.3.6 Ultrasound measurement of the Common Carotid Arteries

There is no statistical power conducted for the common carotid arteries in this study, which explained why the results were all insignificant. Although such

measurement is not readily available in usual clinical practice, it may provide some useful insights into the progression of CVD in insulin resistant patients. However, the period of six months may not show the build up of atherosclerotic plaques as the time frame is too short for deposition of plaques.

### 4.3.7 Availablity of thiazolinediones

There is two thiazolinediones available, pioglitazone and rosiglitazone. In Hong Kong, pioglitazone is only restricted to a certain public hospital and is not widely available. Therefore, rosiglitazone is employed in this study instead. However, recent papers suggested that pioglitazone and rosiglitazone have significantly different effects on plasma lipids independent of glycaemic control. Pioglitazone compared with rosiglitazone is associated with significant improvements in triglycerides and HDL-cholesterol (Goldberg RB et al 2005, Khan MA et al 2002).

## 4.4 Conclusion and Implications for future studies

The challenges faced by clinicians involved early detection of insulin resistance and implementation of treatment strategies that encompass all components of the metabolic syndrome. There is a need to shift the focus in the diagnosis and treatment of the metabolic syndrome from glucose control to primary prevention, early

detection, and treatment of the underlying atherogenic risk factors. This will then prevent the progression of type 2 diabetes mellitus and cardiovascular disease.

Recognition of the relationship between cardiovascular disease and the metabolic syndrome has led to emphasis on appropriate treatment for the metabolic syndrome. To prevent progression to type 2 diabetes mellitus and its complications, lifestyle changes are essential, including dietary therapy and exercise. Drugs which can affect more than one aspect of this syndrome maybe of real value. The potential sparing effects of thiazolidinediones on pancreatic β-cells as well as prevention of diabetes and its complications are promising. This study suggest that with improvements on dyslipidaemia and its insulin-sensitising effects, patients with IGT or type 2 diabetes may respond better to a thiazolinedione as opposed to orlistat or lifestyle intervention. In addition, the thiazolidinediones as monotherapy do not appear to be associated with significant hypoglycaemia or gastrointestinal disturbances. However, comparative clinical studies are needed to clarify whether treatment outcomes with an insulin-sensitiser differ from current therapies. There are no peer-reviewed data available on the long-term effects of the use of thiazolidinediones or much prospective randomized-clinical trials published comparing rosiglitazone with pioglitazone. Further studies regarding the direct head-to-head comparisons of the thiazolidinediones in combination with metformin or

sulphonylurea would also be of interest. The impact of the thiazolidinediones in delaying transfer to insulin and the impact on long-term outcomes should also be considered for investigation.

Orlistat, with its effect on weight, blood pressure, lipids and glucose, may be one of the first drugs that could be placed in the category of a 'metabolic therapeutic agent' (Hollander PA 2002). In accordance to many studies mentioned earlier, this study indicated that even modest weight loss, facilitated pharmacologically or not, produces important metabolic benefits. However, as shown in this study and in the XENDOS study, the addition of a pharmacological treatment with orlistat may be a useful adjunct to dietary and lifestyle intervention in preventing or delaying the onset of type 2 diabetes in obese subjects with IGT or type 2 diabetes. Further long-term studies are required to established if the glycaemic, lipid and insulin secretory metabolic effects of orlistat are sustained and whether the agent has a pharmacological role in reducing cardiovascular event rates in individuals with the metabolic syndrome.

Future studies should be also undertaken to observe the effects of using both orlistat and rosiglitazone in insulin-resistant patients and any additive effects can thus be revealed.

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# Appendices

# Appendices

# APPENDIX I

受試者須知

**INFORMED CONSENT FORM**

**同意書**

Study Title: The effect of Orlistat and Rosiglitazone on insulin action in a group of Chinese patients affected by the metabolic syndrome - a randomized, single-blinded and placebo-controlled study

研究項目: 賽尼可(Orlistat)及羅西格列酮(Rosiglitazone)對代謝綜合徵患者膜島素功能之作用 - 一個隨機單盲安慰劑對照之臨床研究

**Volunteer 自願參加者**

I,_____HKID No._____

address:_____

hereby state that I have read the subject information sheet and I have been fully advised the nature, purpose, procedure and possible risks of the study and have been given the opportunity to question the doctor concerned on all aspects of the study. I understand what is involved and give my consent to participate in the study. I also understand that I can withdraw my consent at any time without giving a reason.

本人,_____香港身份証號碼:居住地址:_____

在此聲明: 我願意參加該項研究我已參閱過「受試者須知」, 完全理解研究者向本人解釋此項研究的性質, 目的, 過程和可能發生的問題, 也明白我可隨時退出研究而不給予任何理由。

Signature of volunteer 志願者簽名: Signature of witness見証人簽名:

_____ _____

Date 日期: Date 日期:

_____ _____

**Investigator 研究者**

I hereby state that I have fully explained the nature, purpose, procedure and possible risks of the participation in this study to the above signed.

本人在此聲明:我已將有關此項研究的性質,目的,過程和可能發生的問題等向以上簽署作了全部解釋。

Signature of investigator 研究者簽名: Date 日期:

_____ _____

# APPENDIX II

## 賽尼可(Orlistat)及羅西格列酮(Rosiglitazone)對新陳代謝綜合症者膜島素功能之作用

## 「受試者須知」

### 1. 研究題目

賽尼可(Orlistat)及羅西格列酮(Rosiglitazone)對新陳代謝綜合症者膜島素功能之作用 - 一項隨機單盲安慰劑對照之臨床研究

### 2. 項目研究者職位 / 機構


| | |
|---|---|
| 李炯前 教授 | 香港中文大學藥劑系 |
| 姚凱詩 副教授 | 香港中文大學藥劑系 |
| 湯寧信 教授 | 香港中文大學內科及藥物治療學系臨床藥理部 |
| 陳重娥 教授 | 香港中文大學內科及藥物治療學系臨床藥理部 |
| 郭志良 教授 | 香港中文大學內科及藥物治療學系臨床藥理部 |


### 3. 研究目的

你已被邀請參與次臨床科學研究,此研究目的是觀察當患有第二型糖尿病或有高度可能演變成糖尿病之癡肥病人，服用賽尼可(一種降低體重之藥物)和羅西格列酮（一種調節血糖之藥物)以後,此兩種藥物對病人膜島素之功能,體重,血壓和血內膽固醇含量之影響。

### 4. 受試者之數目

總數 75 位健康志願者將會被邀請參與是次研究。不論是任何性別患有第二型糖尿病或有高度可能演變成糖尿病之癡肥病人均有資格參與是次研究。有關之受試者均爲威爾斯親王醫院糖尿病診所之病人。

## 5. 研究內容

若你選擇參與本研究,你已經同意以下步驟:
在實驗前,研究者將會對你的病歷詳細詢問,並會對你作一個體格檢查。而研究者亦會從你身上取得血液和尿液樣本,以作血液、電解質、生物化學及肝腎功能檢查(而女性受試者將額外多作懷孕檢查)。這些資料將決定你能否參與此研究。若你能參與研究,研究者會爲你提供飲食指導,而你會在研究期間依足指導飲食。你亦會根據研究者的指示, 服用一種不知之藥物四星期(賽尼可; 羅西格列酮或是沒有藥物成分的藥丸)。四星期之後,你須帶向所有研究用並空藥瓶回診所,而研究人員將會告訴你是否合資格繼續參與研究。若你能繼續參與研究,你會根據研究者的指示,服用一種不知名的藥物六個月(賽尼可; 羅西格列酮或是沒有藥物成分的藥丸)。在服用這種研究之藥物的六個月期間,你須定期回到研究中心,當中研究者會爲你進行體格檢查以及血液檢查以測試膜島素功能,血糖及血膽固醇等。服完所有研究用之藥物後六個月,你會再返回研究中心作多一次如上述之體格及血液檢查。

## 6.實驗中可能產生之不適和不良反應

服用任何藥物皆有潛在的不良反應。從靜脈埋置導管和服用賽尼可以及羅西格列間都可能引起一些不良反應,抽取血液可能引起淤傷、不適、針口發炎和機會較微的感染。

賽尼可會減低脂肪酸的消化並因而減少脂肪的吸收回能幫助降低體重。只有極少量之口服賽尼可會被人體吸收,而它的常見副作用包括排出油膩的糞便並會令病人大便頻繁。羅西格列酮會透過加強細胞對膜島素反應,控制糖尿病人的血糖。只有非常少之情況,它會降低血糖含量(引起心跳加速,出汗,暈眩)。若你對任何研究用之藥物有任何敏感或不良反應,你須明白你不能參與是次研究實驗。同時間參與多個研究可能對受試者構成危險。若你已經參與其他研究,請對研究者詳細報告。除非受試者和研究者同時同意受試者的健康和實驗結果將不會面對風險,否則受試者不能同時參與多個實驗。若受試者已經或將可能懷孕,亦不能參與是次研究,因爲研究可能對胎兒引起不可預知的影響或危險。

## 7. 在實驗中產生之不適和不良反應時的補救措施

靜脈究刺穿及埋置管將由經過訓練者負責,以減低不良反應和不過。在實驗過程中,將有專業研究者對受試者的反應進行檢測;一旦發現不良反應,研究者將會採取相應的醫療措施。

**8. 醫療上的得益**

是次研究會觀察賽尼可和羅西格列酮對膜島素功能的影響,並可能因而會改善一些有關糖尿病的長期併發症,如心臟,腎臟,眼睛之病情。這些資料對日後決定對患有第二型糖尿病或有高度可能演變成糖尿病之癡肥病人的治療,有重要的意義和作用。

**9. 對受試者的報酬**

你並不會因爲參與及完成整個研究而獲得任何金錢的報酬。

**10. 私隱及保密**

受試者身份將不會在此研究任何報告中發表。而有關的資料、個人資料、記錄將會被保密,並受香港法律保障。

**11. 對身體不適的處理**

本項目之研究者隨時願意爲受試者解答有關本研究的問題。若受試者有任何疑問或因本研究引起不適,可隨時與下列人士聯絡。

李炯前(地址:香港中文大學藥劑系,電話:26096827)

湯寧信(地址:香港中文大學內科及藥物治療學系臨床藥理部,電話:26323139)

**12. 參與研究的自願性**

受試者之參與爲自願性。你可以拒絕、或在任何時間退出此研究,而不會受到任何懲罰。

**13. 同意書**

此文件的其中一份副本將存於研究者記錄以作備案。而另一份副本則交與受試者。

## APPENDIX III : Clinical Record Form (CRF)

Name: _____ ID No.: _____ Tel No.: _____

Gender: _____ Age: _____ D.O.B: _____

Screening #: _____ Consent: Yes / No Randomisation #: _____

Date: _____ Visit #: _____

Body Weight: _____ kg Body Height: _____ cm BMI: _____ $kg/m^2$

Time: _____

| Sitting BP | 1st Reading | 2nd Reading | 3rd Reading |
|---|---|---|---|
| Systolic | | | |
| Diastolic | | | |
| MAP | | | |
| Heart Rate | | | |

Urine Test: Protein: _____ Glucose: _____ RBC: _____ Ketone: _____ pH: _____

Drug Allergy: _____

Blood Test today; Dietary Advice: Y / N MRI Scan: Y/ N

OGTT : Y / N Urine Pregnancy Test : Y / N / NA Physical Examination: Y/ N

Past Medical History: _____

_____

_____

Current Medications: _____

_____

_____

Adverse Events:

Symptom: 1. _____ 2. _____ 3. _____

Date Started: 1. _____ 2. _____ 3. _____

Treatment: 1. _____ 2. _____ 3. _____

End Date: 1. _____ 2. _____ 3. _____

| Study Drug Given: | Morning: | Lunch: | Dinner: |
|---|---|---|---|
| Study Drug Returned: | Morning: | Lunch: | Dinner |
| Study Drug Missed: | Morning: | Lunch: | Dinner: |
| Compliance: | | | |

Investigator's comments: _____

* Anthropometric measurements were recorded on a separate table not shown here